

**THE INFLUENCE OF SERUM MAGNESIUM LEVELS ON BRAIN TISSUE
OXYGENATION AFTER SEVERE TRAUMATIC BRAIN INJURY**

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Traumatic brain injury is one of the leading causes of morbidity and mortality in the United States. A number of different pharmacological and therapeutic based clinical trials have proven to not be efficacious for reversing these trends. In fact, many of these clinical trials have had deleterious effects on patient outcome. Clinical trials with magnesium supplementation are included in this group. The routine use of magnesium may increase the likelihood of secondary hypoxic and anoxia events in these patients, therefore leading to increases in morbidity and mortality in a number of patient populations.

The purpose of this study was to investigate the effects of magnesium supplementation on cerebral oxygen tension levels after closed head injury. Nineteen severe head injury patients, who had both cerebral oxygen probe placement and magnesium supplementation within the first 48 hours after injury were included in this study. All interventions were performed under patient consent and Institutional Review Board approval. The cerebral vascular response to magnesium varied by patient, with some patients having dramatic losses or gains in oxygen levels, while others were unaffected. Since only two female patients were included in this group, statistical analysis of data was restricted to the males of the study group. Overall cerebral oxygen levels were clinically unchanged during magnesium infusion periods (27.698 mmHg versus 24.886mmHg) using a mixed model regression adjusting for cerebral perfusion pressure, time after a magnesium infusion and percent of inspired oxygen ($p \leq 0.0001$). An additional model was constructed controlling for the same variables to investigate the impact of the magnesium dose on tissue oxygenation. Only doses of two or four grams of magnesium improved brain tissue oxygenation ($\beta=8.980$ and 8.500 respectively $p \leq 0.001$). In conclusion magnesium infusions are not adversely affecting tissue oxygen levels after head injury and a dose of four grams or less during actually improve oxygen levels. The public health significance of this study is that the

routine use of intravenous magnesium supplementation may exacerbate tissue injury in patients with impaired blood flow to the brain. The resulting increases in the mortality and morbidity to brain injury patients would have an enormous economic and social cost.

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PREFACE

Nomenclature used: NMDA=n-Methyl-d-Aspartate; CPP=Cerebral Perfusion Pressure; VSCM=Vascular Smooth Muscle Cell; CSF=Cerebrospinal Fluid; ECF=Extracellular Fluid; MASH= Magnesium and Acetylsalicylic acid in Subarachnoid Hemorrhage study; IMAGES= Intravenous Magnesium Efficacy in Stroke; PUH=Presbyterian University Hospital; GCS=Glasgow Coma Scale; EVD=Extraventricular Drain; MARS=Medical Archival Systems; ICU=Intensive Care Unit; IV=Intravenous; mEq/L=Milliequivalents/ Liter; FiO₂=Fraction of Inspired Oxygen; PbTO₂=Partial Pressure of Tissue Oxygen; CT=Computer Axial Tomography; MAP=Mean Arterial Pressure; ICP=Intracranial Pressure; BTRC=Brain Trauma Research Center; UID=University Identification; GOS=Glasgow Outcome Scale; PDS=Patient Data Server; MVA=Motor Vehicle Accident; SDH=Subdural Hematoma; SAH=Subarachnoid Hematoma; NICU=Neurointensive Care Unit; UVPM=Bedside monitor designation of Licor values; EDH=Epidural Hematoma.

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1.0 INTRODUCTION AND SCIENTIFIC BACKGROUND

Head injury is one of the leading causes of mortality and morbidity in the United States. The major focus of post-injury treatment in head trauma victims is the reduction of secondary injuries to the brain in the hours and days after the initial traumatic injury. Secondary injuries can propagate through the brain as mechanical and apoptotic cell deaths release ever-increasing amounts of biochemicals and free radicals into the neuronal environment. These fundamental changes to the interstitial fluid leave neurons teetering on the edge of life and death. Therefore, it is absolutely essential to optimize post-traumatic treatment to ensure adequate supplies of blood and oxygen to the brain tissue as a whole, and especially that tissue closest to the injury, termed the penumbra. Recently, magnesium supplementation therapy has garnered attention as a vasodilator and neuroprotective agent after brain injury in an attempt to improve neurological outcomes.

Magnesium is an essential trace metal for normal bodily and cellular function. Bone is the major storehouse for magnesium in the body (Ebel 1980). Ionized magnesium can be liberated from bone to the extracellular fluid, where it can be used as a cofactor in enzymatic reactions (Ebel 1980). Magnesium is also essential to ATP production in cells (Ebel 1980, Jacobash 1977). Since magnesium is essential for energy production, a lack of free intracellular magnesium can lower the cellular anabolic processes (Teraski and Rubin 1985).

Magnesium ions have a particularly vital role in the regulation of neuronal impulses in the central nervous system. Meltzer and Auer reported the paralysis of rabbits with intracerebral injections of magnesium sulfate, which could be reversed by injections of calcium ions (Meltzer and Auer 1908). This inhibitory effect of magnesium is a reflection of the antagonistic relationship magnesium and calcium share throughout the body. It is, however, gravely important to normal neuronal functions. Glutamate is a major excitatory neurotransmitter in the brain, and its n-methyl-d-aspartate (NMDA) receptor is blocked by magnesium (Nowak et al. 1984 and Marrets et al.1995). The NMDA receptor has long been theorized to be a primary entry point for calcium into neurons in the after trauma. Magnesium and calcium influx can determine the amount of acetylcholine released from presynaptic neurons (Krapivinsky et al. 2006). The cellular level effects of magnesium have consequences for the entire body. Therefore, the interplay between calcium and magnesium ion fluctuations after brain injury is critical to neurological outcome.

1.1 EXPERIMENTAL EVIDENCE

Magnesium's essential intracellular functions have led to a myriad of animal experiments to examine the magnesium response to trauma. Bareyre et al. showed that the level of serum magnesium after trauma was predictive of outcome in rats (Bareyre et al. 1999). In this experiment, serum magnesium depressions could safely be raised by supplementation with magnesium compounds without any affect to the cardiovascular system (Bareyre et al. 1999). Other studies have shown that magnesium injections prior to injury were associated with hyperglycemia, larger ATP loss, greater acidosis, and lower heart rate (Blair et al. 1989; Gee et

al. 2004). When giving magnesium prior to injury, however, the dose and type of magnesium may influence the outcome after trauma (Miles et al. 2001). Westermaier et al. found that pre-injury doses of magnesium caused a transient depression in MAP and heart rate (Westermaier et al. 2005). In addition, it was found that slow infusions are better than bolus infusions for the recovery of blood flow after experimental occlusion (Westermaier et al. 2005).

Intracellular magnesium loss is a hallmark of traumatic brain injury. Rat studies have shown that Mg^{2+} shows a persistent decline after trauma (Vink et al. 1988). CSF total magnesium has been shown to be predictive of outcome in humans (Fischer et al. 2006). The predictive value of serum and intracellular magnesium are well proven in animal and human models after injury (Bareyre et al. 1999; Lampl et al. 1998; Miles et al. 2001; Vink et al. 1988). In addition to effects on neurons, magnesium has a known influence on the cerebral vascular tone.

1.2 PHYSIOLOGICAL RATIONALE FOR AND THE USE OF MAGNESIUM IN CLINICAL TRIALS

Cerebral perfusion pressure (CPP) is a non-invasive measure of the pressure of blood flow through the entire brain. In closed head injuries, the swelling brain has very little room to expand. As the brain swells into the skull, the pressures exerted on the brain tissue increase, providing a force acting to narrow cerebral arteries, and restrict blood flow to the tissue. Extraventricular drains can be used to measure and relieve pressures associated with herniation. CPP is calculated as the difference between the mean arterial pressure and intracranial pressure

at any given time point. It has been recommended that CPP be maintained at 60mmHg or above in order to ensure adequate blood supply to the brain (Juul et al. 2000).

Declines in CPP as little as 10mm Hg can affect mortality as much as twenty percent (Bullock et al. 1995). As cerebral perfusion pressures fall, the risk of hypoxic insult to the brain increases (Marin-Caballeros et al. 2005). Since neurons maintain ionic gradients for synaptic transmission, they are especially sensitive to ischemic episodes where there is a failure of cellular energy stores (Rothman 1983). Magnesium supplementation has been shown to protect neuronal cultures from anoxia due to ischemic episodes (Rothman 1983). Head injury patients with normal levels of ionized magnesium in their blood are more likely to have an improved neurological outcome (Stippler et al. 2006). The biochemical and physiological effects of magnesium on the brain are critical in the acute post-traumatic period. Altura et al. have shown that rats deficient in magnesium had greatly increased arterial pressures due to a 33% increase in vasoconstriction (Altura et al. 1984). This may be due to alterations in management of blood lipid levels, which are associated with serum magnesium levels (Altura et al. 1990).

Lack of magnesium was associated with greater contractility of vascular smooth muscle cells (VSMCs) in response to norepinephrine in a dog artery model (Turalapaty and Altura 1980). In addition, the VSMCs of hypertensive rats have less magnesium than non-hypertensive rats (Touyz et al. 1998). Even normal rats fed a magnesium deficient diet had higher intracellular calcium ion levels, which would allow for prolonged vasoconstriction (Touyz et al. 1998). Magnesium supplementation has been shown to increase cerebral oxygenation by 34 percent after aneurysm clipping (Chan et al. 2005).

1.2.1 Magnesium and the Brain

Magnesium levels in the cell are tightly regulated under normal conditions. In the normal brain, the uptake of peripherally administered magnesium is sluggish (Opplet et al. 1963). Even with serum magnesium levels elevated 3 to 4 times normal levels for hours there was only about a 20% increase in magnesium in the cerebrospinal fluid (CSF) (Opplet et al. 1963). The exchange between the extracellular fluid (ECF) and cells leads to a relatively constant interstitial and intracellular magnesium level (Romani 2006). Once inside the cell, the divalent positive charge of ionized magnesium allows it to bind to negatively charged molecules. This binding leads to a compartmentalization of bound magnesium into organelles such as the mitochondria and endoplasmic reticulum (Romani 2006).

The depressed levels of serum magnesium after head injury have many potential causes. These include the use of osmotic agents (which increase renal magnesium loss) the use of magnesium free IV fluids and loss of blood (Polderman et al. 2000 Kahraman et al. 2003). Supplementation of magnesium into the blood therefore should restore normal serum magnesium levels, while also protecting the injured brain. Magnesium reaches the brain slowly at best under normal conditions and may reach the brain in miniscule amounts under traumatic conditions. McKee et al. have shown that magnesium enters the brain slowly after trauma, with only a fifteen percent increase after twenty-four hours of hypermagnesemia (McKee et al. 2005). It was also found that magnesium entry into the CNS varies according to the type of injury, with closed head trauma having the smallest increase (McKee et al. 2005). In a study of magnesium versus nimodipine in subarachnoid hemorrhage, the CSF levels of ionized magnesium were unaffected by supplementation (Schmid-Elsaesser et al. 2006). Therefore, the intended purpose for magnesium supplementation may never be realized and the potential deleterious effects to

cerebral blood flow may actually make supplementation worse. Stippler et al. have shown that patients with low serum magnesium levels that are corrected inside 24 hours actually do significantly worse than those patients who are not corrected (Stippler et al. 2006).

1.2.2 Magnesium in Clinical Trials

The use of magnesium as a therapeutic agent to prevent neuronal loss after traumatic injuries to the brain has not yet proven effective in clinical trials. The magnesium supplementation group of the Magnesium and Acetylsalicylic acid in Subarachnoid Hemorrhage (MASH) trial has been shown to have significantly better outcomes, but supplementation did not affect the number of poor outcomes or delayed cerebral ischemic events (van den Berg et al. 2005). Wong et al. have found that magnesium supplementation did not improve the number of good outcomes but that it did reduce the length of vasospastic episodes in subarachnoid hemorrhage patients (Wong et al. 2006). Other small randomized trials have proven that the circulatory effects of magnesium supplementation in stroke patients were not significantly different from placebo. Also, the outcome of patients was not significantly changed (Muir et al. 1995; Muir et al. 1998).

The largest clinical trial yet completed on magnesium therapy, the Intravenous Magnesium Efficacy in Stroke (IMAGES) trial, failed to show any significant change in outcome with magnesium. In fact, there was a slightly higher mortality in the magnesium group (Lees et al. 2004). This trial consisted of over two thousand patients and the only positive change in outcome was seen in a small lacunar stroke population (Lees et al. 2004). Is magnesium therapy for the treatment of brain injury dead with this trial? Arango and Mejia-Mantilla have done a review of all major magnesium trials and found no evidence of a benefit to magnesium supplementation (Arango and Mejia-Mantilla 2006). The recently published study by Temkin et

al., showed magnesium supplementation to worsen neurological outcomes and increase mortality rates in head injury patients (Temkin et al. 2007).

Why has magnesium supplementation been shown so effective in small clinical trials, but as ineffective or even deleterious in larger clinical trials? The answer most likely relies on how the individual patients respond to magnesium. As the population sampled grows, so does the variance in the response to magnesium supplementation. Since vasoconstriction and pressure from the swelling brain will act to constrict the cerebral vasculature, a vasodilator, like magnesium, should improve cerebral oxygenation. This improvement has been shown to occur in aneurysm patients after a brief period of vessel occlusion (Chan et al. 2005).

1.2.3 Specific Aims

The increases in mortality and morbidity caused by magnesium supplementation in clinical trials presents a conundrum for the treatment of head injury patients, who are commonly given magnesium in order to augment serum levels (Lees et al. 2004; Temkin et al. 2007). Patients who are supplemented for serum magnesium levels below the normal range within the first 24 hours after traumatic brain injury have significantly worse outcomes than those patients who are not supplemented (Stippler et al. 2006). Given these potential problems with magnesium administration and its properties as a vasodilator, the purpose of this study is to investigate the effects magnesium infusions have cerebral oxygen levels after traumatic brain injury.

2.0 MATERIALS AND METHODS

The patient population for this study consists of patients admitted to Presbyterian University Hospital (PUH) with a closed head injury, Glasgow Coma Score (GCS) of 8 or less and who are admitted to the hospital within the first 48 hours after the time of the injury (Figure 1). In addition, these patients must have an extraventricular drain (EVD) placed, a Licox probe to measure cerebral oxygen tension, and a dose of magnesium sulfate. A closed head injury is any injury not involving a penetrating foreign body. Therefore, the brain can be exposed to the ambient air, and patients with injuries such as depressed skull fractures will be accepted. On the GCS scale, a score of 8 or less indicates a severe level of neurological impairment. A patient can qualify for the study if his/her GCS score upon hospital admission is 8 or less, or if the patient is admitted to the hospital with a GCS above 8 and later his/her condition deteriorates. Patients in the latter category are usually brought in from outside hospitals and thus are unlikely to have met the criteria for acceptance into this study before the end of the 48 hour period.

Glasgow Coma Scale (GCS):			
EYES	Open	Spontaneously:	4
		To verbal command:	3
		To pain:	2
		No response:	1
BEST MOTOR RESPONSE	To verbal command	Obeys:	6
	To painful stimulus	Localizes pain:	5
		Flexion-withdraw:	4
		Flexion-abnormal:	3
		Extension:	2
		No response	1
BEST VERBAL RESPONSE		Oriented and converses:	5
		Disoriented and converses:	4
		Inappropriate words:	3
		Incomprehensible sounds:	2
		No response:	1
TOTAL			3-15

Figure 1 Glasgow Coma Scale

Glasgow Coma Scale scores for eye opening, motor response and verbal response.

The initial 48 hour period after injury has been chosen since this is a critical time for averting secondary injuries to the brain (Bullock et al. 1995). The significance of using this time period for physiological monitoring is that this is the most likely time for ischemic events, and magnesium therapy has been theorized as being critical in this early time period (Lees et al. 2004). With recent clinical studies and trials showing magnesium supplementation worsening

neurological outcome, the efficacy of serum magnesium replacement in the traumatic brain injury population needs examining (Temkin et al. 2007, Stippler et al. 2006). Since magnesium is theorized to influence vasodilation at the arteriole and venule level, tissue oxygenation should be directly effected by magnesium supplementation (Belfort et al. 1999). This vasodilatory effect may lead to hypoperfusion and subsequent anoxic insult to the brain. Therefore this study focuses on the affect of the of magnesium supplementation on Licox values in patients given magnesium sulfate to augment low serum magnesium levels.

2.1 DATA SOURCES

The data collection for this study is being achieved through the use of multiple sources. Presbyterian university hospital maintains secured online databases that store patient medical records (MARS) and bedside records of treatment on intensive care unit (ICU) patients called EMTEK. In order to determine the effect magnesium has on a patient's Licox values, the exact time of initiation of the medication, as well as the dose, must be obtained. The MARS database lists records of every medication given, the dose, and the start time of the medication. MARS relies on the bedside nurse to obtain this information and, therefore, the EMTEK records will be the ultimate source for medication times. For each medication that is not given as a continuous infusion, the bedside nurse lists the time, type and dose of the medication. This is done by scanning the admission bracelet of the patient and then the medication's pharmacy bar code, which logs the information into the bedside computer. This system minimizes the risk for improper dosage and medications. The exact end time of the medication is a rough estimate, given the infusion rate and the volume of the medication. Since these patients are paralyzed and

sedated, the route of medication administration is by intravenous (IV) access. This may constitute directly syringing the medication through the central IV line or by IV bags. Magnesium infusions occur by the latter method. Since magnesium is infused by bag, it is possible to have unrecorded periods when the medication is stopped, but the magnesium dose should finish fairly close the actual time prescribed by the magnesium protocol (Table 1). Adherence to this protocol will consist of not only the dose, but the time over which the dose is given. In order to determine the proper dose, all patients will have their serum magnesium levels recorded, and this will be the primary determinant of whether the dose is appropriate.

Table 1 Magnesium Replacement Protocol

Magnesium Level (mEq/L)	Magnesium Sulfate Dose (IV)	Infusion Rate	Recheck Level After Infusion
1.5-1.9	4 grams	Over 2 hours	In AM
1.0-1.4	8 grams	Over 4 hours	In AM
<1.0	8 grams	Over 4 hours	4 hours

Magnesium replacement protocol for the neurointensive care unit at the University of Pittsburgh.

MARS and EMTEK are also being used to obtain data on the patients' care and injury history. Included in the MARS database are records for ventilator settings. Whenever there is a change in a patient's ventilator care, the entire set of settings on the ventilator is recorded as well as the time and date. The ventilator setting that has the most profound effect on Licox values is the fraction of inspired oxygen (FiO₂) (Figure 2). The viability of a Licox probe is tested, once it is placed in the brain tissue, by changing the FiO₂ level to 100% for a short period of time and seeing if there is a subsequent increase in cerebral oxygen levels. The response is often rapid,

thus indicating the viability of the probe, and the ventilator is reset to the original settings. Given this ability of FiO₂ to influence the Licox value, it is expected that some patients will be managed for low cerebral oxygen tension (Licox values) by manipulation of the FiO₂ setting (Figure 3).

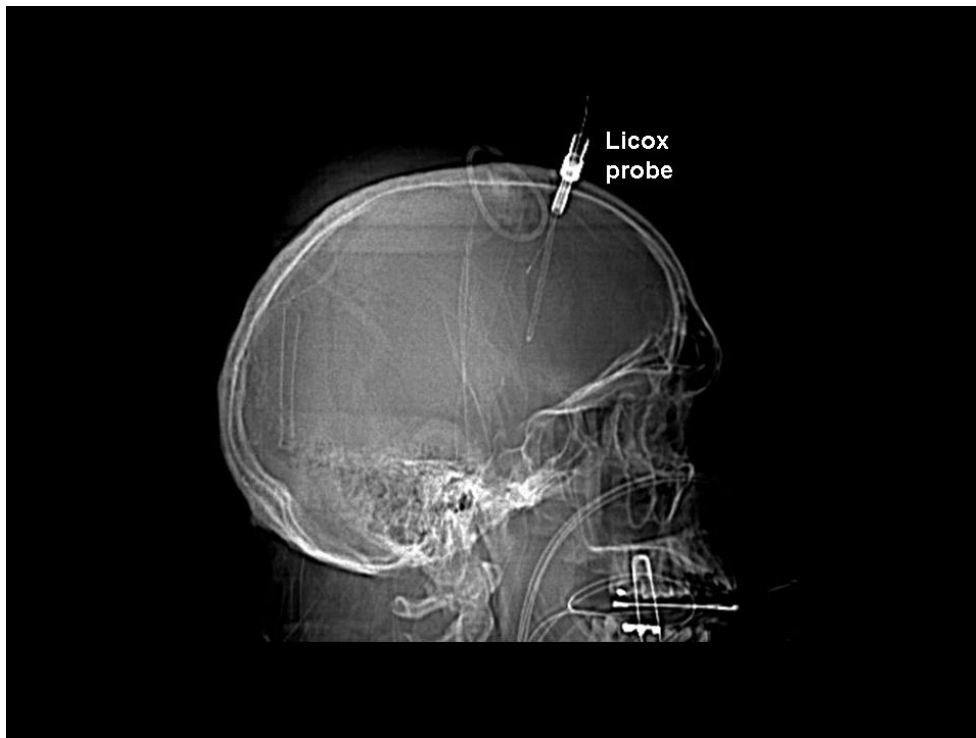


Figure 2 Licox Placement Oblique View.

CT scan image of Licox probe trajectory into the brain in a trauma patient.

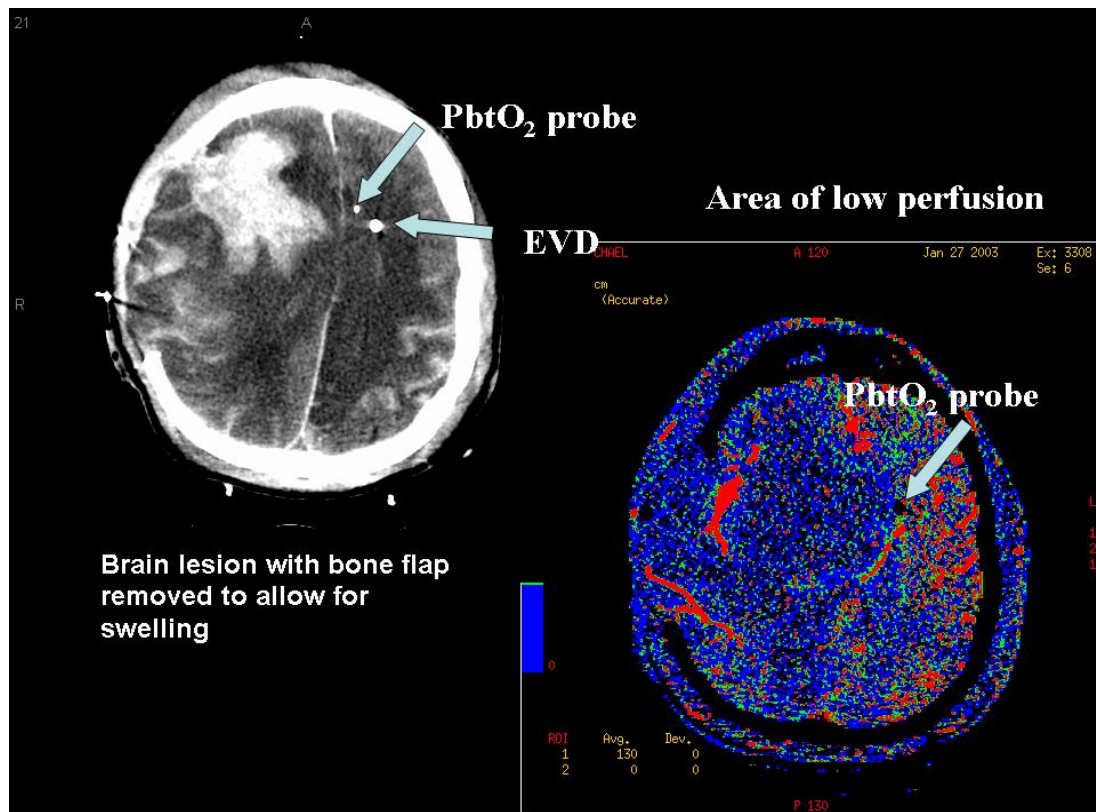


Figure 3 CT Scan of Brain with Blood Perfusion Data Shown.

This is a CT scan of a brain tissue injury showing location of Licox (PbtO₂) probe and the EVD. The bright white areas in the brain are the hemorrhagic regions of the brain. Also pictured is a Xenon CT scan showing areas of poor blood flow in blue.

The results of all Computed Axial Tomography (CT) scans will also be obtained from MARS. The radiologist's impressions of the initial scan will be recorded and designated as the primary neurological injury. The reports consist of a description of the areas of the brain affected and what type of injury persists in that area. This is followed by a brief description of the injuries in bullet form fashion. Both areas of these reports will be utilized, since injuries that are considered lesser at the time of the initial CT scan can erupt into larger injuries at a later date. In addition, the Marshall score will be given when available. This score is a measure of the severity of the injury and is prognostic of outcome (Marshall et al. 1991). The Marshall score

attempts to quantify the amount of swelling in the brain by scoring for the presence or compression related absence of specific anatomical brain regions (Marshall et al. 1991).

Marshall Diagnosis Score for CT scans:

- 1: No visible intracranial pathology seen on CT.
- 2: Cisterns present with shift of 0-5mm/Lesion present.
- 3: Cisterns compressed or absent with shift 0-5mm, no lesion >25cc.
- 4: Midline shift >5mm no high or mixed density, lesions >25cc.
- 5: Any lesion surgically evacuated.
- 6: High or mixed density lesion >25cc, not surgically removed.
- 8: Primary brain stem lesion.
- 9: unknown.

Figure 4 Marshall Score Diagnosis Scale.

Marshall diagnosis for severity of brain trauma on CT scans.

EMTEK will be used to note all times when blood transfusion are given to the patients. There is no evidence that blood transfusion directly influences Licox values. However, transfusions will increase blood volume, and therefore, impact other physiological variables like mean arterial pressure (MAP), CPP and possibly even intracranial pressures (ICP). MARS includes no records on blood transfusions, since blood products are the obtained from the Central Blood Bank and not the hospital itself. Therefore, EMTEK will be the only source for the time of transfusion and the number of units transfused.

For all demographic, surgical, complications and interventions data, the Brain Trauma Research Center (BTRC) will be the primary source. This database is the main database for the National Institute of Health grant that funds the research performed on closed head injury at

PUH. All patients that come to the hospital with a GCS of 8 or less and a non-penetrating brain injury are assigned a University Identification Number and (UID) and general demographics are obtained, such as name, initial GCS and mechanism of injury. All families of the patients are approached to obtain consent for study procedures, and only those patients who have family obtained consents were considered for this study.

The primary data sources for this study are demographics, surgery complications, emergency department records, outcome databases and physiological databases, which are part of the main BTRC database. Data that are beyond the time frame or scope of this study will not be used, but all other data will be used to provide a detailed description of how the patient was injured and how the patient was cared for in the ICU. There will be two main demographic files: the surgical and general demographic file. The general demographic file will have information on all aspects of the patient's background, injury history, and complications. The surgical database will have detailed records of surgeries performed. The need for this separation of demographics is the fact that all patients are likely to have multiple surgeries on multiple organ systems, due to the nature of how the patients are commonly injured. Data considered beyond the scale of this study are those that would not directly affect outcome or Licox values directly. The notable exception is the outcome database which records the Glasgow Outcome Scale (GOS) scores for each patient at 3, 6, 12 and 24 months (Figure5). Since the physiological trends and data trends of each patient will directly portend the patient's eventual outcome, these data are critical to this study. The primary neurological outcome time will be the three month GOS. While patients can go up or down one point on the GOS scale as time progresses, two point swings in either direction are rare. In the case of a later death, these changes are often not related to the head injury, but other injuries suffered in or due to the original accident.

Glasgow Outcome Scale (GOS):

- 1: Dead
- 2: Vegetative
- 3: Severely Disabled
- 4: Moderately Disabled
- 5: Good Recovery

Figure 5 GOS Scale.

All data on physiological parameters will be obtained from the Patient Data Server (PDS) arm of the main BTRC database. Data are obtained by linking the monitors at each of the patient beds on the NICU to a network, where the server has access to download the data. Data are downloaded and then posted to a program that cross lists all of the physiological parameters according to the minute they were recorded from the unit. These data are then “cleaned” by a nurse to remove any spurious data that can result from normal patient activities interfering with the proper functioning of the various monitoring probes. Given this restriction, there is a limited pool of patients available for this study. The use of the Licox probe began in February of 2002 and the last clean data were posted around the end of 2005. In that time period, 154 patients were enrolled in the BTRC study and of those patients, 28 met the qualifications of having Licox probes, a valid consent, cleaned data, and being housed on a unit wired for the PDS. Of these 28 patients, 19 had a magnesium dose within the first 48 hours.

2.2 PATIENT MANAGEMENT IN THE ICU SETTING

2.2.1 Admission Protocol

The care of all severe head injury patients is governed by the Physician Orders. These orders set up four different protocols that direct patient care from admission to discharge from the ICU. The first protocol covers patient hospital admission. The aim of this protocol is to maintain an environment for the patient so as to minimize the potential for secondary insults to the brain (Figure 16A). In order to minimize this risk, the primary concern for patients placed on this protocol is to sustain the various physiological parameters within their prescribed ranges. Determining whether the protocol was followed hinges on whether the patient remains in these physiological ranges. All patients will be checked to assure that the prescribed medications are given, but since these medication are ancillary to the physiological maintenance, only egregious violations of the medication and infusion sections will serve as a reason to deem the patient not in compliance with the protocol. Patients who are not maintained in these ranges but are being treated to return their physiological variables to normal ranges are considered in compliance with this protocol, as deviations are the norm for this patient population. Therefore, a patient can only fail the admission protocol if he/she failed any of the other protocols or is hyperthermic for an extended period of time.

2.2.2 Intracranial Hypertension Management Protocol

The next portion of the admission orders deals with the intracranial hypertension protocol (Figure 17A). This protocol is meant to outline the treatment of intracranial hypertension (high

ICP values). Intracranial hypertension is defined in the protocol as an ICP value of greater than 25 mmHg. The primary point of determining adherence to this protocol is deciding on the use of mannitol and hypertonic saline, which are diuretic agents intended to lower ICP values by increasing urine output. Often, mannitol is used as a first line of treatment for patients whose ICP values are above 20, but not quite sustained for any long periods at or above 25 mmHg. Therefore, its use indicates that the patient is aggressively being treated for elevated ICP values and this is the underlying intention of the protocol.

The third protocol is the sedation protocol (Figure 18A). Patients are paralyzed and sedated to minimize the risk to the patient and staff. Often, head injury patients are combative and this exertion can harm the staff, as well as massively disrupt the patient's physiology. Adherence to this protocol is determined by the administration of propofol, fentanyl and vecuronium. If these drugs are not given, then the patient will be deemed not in adherence.

The final protocol in the physician's order set is the fluid replacement protocol (Figure 19A). Adherence to this protocol is determined by the use of normal saline, albumin, hetastarch and Levophed infusions. Levophed is a trade name for norepinephrine or adrenaline. Its use increases heart rate and cardiac output and therefore improves blood flow. Any patient that is hypoperfused or in a hypotensive state and is not given fluid/colloidal replacement and or Levophed will be deemed not in compliance with the protocol.

2.2.3 Importation into SAS

Data is being imported into SAS using three separate Excel files that will combine a coded version of the patient and surgical demographics with a file containing the physiological data for

each patient for the first 48 hours. In order to achieve this goal, each patient's individual physiological records are being combined into a single Excel file and then the demographic data is being programmed into SAS to form a single file that can be analyzed for the influence on Licox values. The physiological file contains the following variables: university identification number, time, Licox values, serum magnesium value, fraction of inspired oxygen level, the time of red blood cell transfusions, mean arterial pressure, intracranial pressure, core temperature, cerebral perfusion pressure, and time, which will be negative before a magnesium infusion, zero when the infusion begins, and positive thereafter. Finally, the file includes the duration of magnesium infusions. The following demographic variables will be added to the physiological data: magnesium dose, time from injury to magnesium dose, magnesium protocol adherence, injury type, injury side, Alsius, age, gender, GCS, complications, mechanism of injury, transportation type, emergency department drugs, Marshall score, and 3, 6, 12 and 24 month outcome.

The file includes all patients. However, the analysis is being restricted to males only, since there are only two females in the data set. This same logic was applied to the coding of the demographic and surgical data in order to have sufficient patient numbers in each group. The notable exception is the variable coding for emergency department drugs. A code was given to norepinephrine administration in the emergency room despite the fact that only one patient was treated with norepinephrine. The reason for coding this lone norepinephrine patient is that this drug is a treatment for hypotension. Patients who are hypotensive on admission often suffer secondary hypoxic events that would influence Licox levels. Injury type comprises the main injury types, which for this patient population are subarachnoid hemorrhages (SAH), subdural hemorrhages (SDH), or combined in the case of multiple injuries. Intracranial contusions are not

considered for entry because of the great variability among the patients. The complications variable is being coded as either nonexistent, non-neurological or neurological in nature. This variable is limited by the fact that while the complicating event is noted, the time of the complication is not. Since the time of each complication is vital to any influence this variable would have on Licox values, this variable will not be considered for inclusion in the model. There are three mechanisms of injury considered: motor vehicle accidents, motorcycle accidents and other. The surgical variable will be dichotomized to none/non-neurological surgery, or a surgical procedure involving the brain. Procedures performed on the brain are most likely to have a direct effect on cerebral oxygen tension values, and since these are multiple trauma patients, multiple surgeries are likely to occur making multiple coding difficult in this small patient population.

2.2.4 Statistical Modeling of the Data

The lack of females in this data set makes analysis of the female response to magnesium after brain injury impossible. Also, there is a known disparity in neurological outcome between men and women after brain injury (Farace and Alves 2000). Further complicating the matter is the large disparity in age between the women. One woman is 43 years old and the other is 16, intimating that the estrogen levels in these women could be wildly different and the corollary being that both their brain and body chemistries will be completely different. There is also evidence that the effects of serum magnesium vary between men and women (unpublished data). In addition, there may be gender differences in magnesium metabolism after head injury, as women have significantly lower magnesium levels than their age- and injury-matched male

counterparts (unpublished data). Therefore the analysis for this data set will be restricted to the males in the population.

Analysis of the data set is complicated by the fact that cerebral oxygen levels may vary by the complexity of the patients' injuries and medical care and by unmeasurable variables like genetic variation. In planning the analysis of this data set there were three models types considered potentially useful. General estimating equations (GEE) specify marginal models, which allow for generalizing the results of the analysis to an entire population (Ballinger 2004). Also, GEE models can be employed with data a continuously distributed response variable (Fitzmaurice et al. 2004). Finally, these models are robust against misspecification of both the distribution of the response variable and the correlation structure of the model (Ballinger 2004). The major problem with GEE models as it pertains to this data set is the requirement that missing data be missing completely at random (MCAR) (Ballinger 2004). However, missing values in this data set are often the result of the conditions under which they occur. A patient who is suffering from an epileptic seizure will have nonsensical or missing oxygen values that are interspersed with data that look completely normal. Missing data in this data set are also commonly caused by bedside procedures that are the direct result of low cerebral oxygen values. Therefore, since the missing values of this data set are not MCAR, GEE models can not be used for this data set.

The next consideration for modeling this data was to use time series analysis. Of the different types of times series analysis available, time series cross section regression seemed the most applicable to the analysis goals of this study. This type of time series analysis allows for the modeling of both fixed and random effects (SAS Institute 1999). The major drawback is that balancing is required to for the time series for each cross section, and the time period for the

cross section variable must be the same for all time series (SAS Institute 1999). This is not the case in this data set. Patients are routinely removed from the unit for surgical and diagnostic procedures. Thus, these data are quite unbalanced.

The final model considered for this data set, and the one that will be used, is linear mixed modeling. Mixed models allow for the use of both fixed and random effects and the specification of the correlation structure (Fitzmaurice et al. 2004). In addition, these mixed models allow for the analysis of continuous dependent variables, which is of primary importance for this analysis given the nature of cerebral oxygen values. Linear mixed model regression assumes that the error terms and random effects are normally distributed with a mean of zero. Additionally, the random effects are assumed independent for each person and for the error terms (Laird and Ware 1982). The requirement for normally distributed residuals is a problem for the analysis of these data. Previous attempts to analyze minute by minute physiological data have shown that the residuals are often non-normal. The primary problem leading to this non-normality is the extreme kurtosis that is often associated with this type of data. The data tend to cluster around a central range of values (Figure 9). A variety of different transformations, including log and power transformations, were done on this data set in order to obtain normal residuals. However, none of the transformations were able to produce normalized residuals. Since the non-normality of the residuals will affect the various model p-values, the results of this study must be interpreted cautiously.

Since the use of cerebral oxygen monitors is still relatively new, all relevant variables were considered for inclusion in the model. The first step in the modeling process was to model Licox values against magnesium infusion and time, thus giving a baseline estimate of the effect of magnesium dosing on Licox values (Figure 6). The next step was to begin building the final

adjusted model for the data set. Age and GCS have a known association with outcome after severe head injury. There is, however, no evidence of an effect for either of these variables on cerebral oxygen levels (Bullock et al. 1995). Therefore these variables were not considered for a priori inclusion in the model. Also, while considering physiological variables to include in the model, MAP and ICP were excluded due to their relationship with CPP. The use of CPP allowed for the effects of ICP and MAP to be accounted for while avoiding any potential problems with collinearity. The variables that were considered for inclusion in the model are as follows: FIO₂, CPP, the magnesium dose, the type of injury, the side of the brain where the injury is located, GCS, age, Marshall score, surgery, complications, adherence to the magnesium, ICP, sedation and fluid replacement protocols (Table 2). The data were first modeled using an unstructured correlation structure and upon examining the correlation matrix, an autoregressive correlation structure appeared to be appropriate for the data. Therefore the data were modeled using a random intercept and an autoregressive correlation structure. For the magnesium infusion variable the model estimated a parameter for periods when infusion did not occur and periods of magnesium infusion were taken as the baseline of the variable.

$$E(Y_{ij} | b_i) = \beta_1 + \beta_2 \text{Mginfusion}_{ij} + \beta_3 \text{Time}_{ij} + b_i + e_{ij}$$

Figure 6 The Equation for Base Model for Licox Values

This equation shows the mean Licox response for the base model for the i^{th} individual at the j^{th} time adjusted for magnesium infusion and time. The model assumes random subject effects (b_i) and error terms (e_{ij}) are both normally distributed with a mean of zero. Also the model assumes that the random subjects effects are independent for each subject and for the error terms. β_1 = intercept parameter estimate; β_2 = magnesium infusion parameter estimate; β_3 = time parameter estimate.

Table 2 Description of Variables Considered for the Final Model

Variable	Description of the Variable	Variable type
FiO2	Fraction of oxygen inspired by the patient	ordinal
CPP	Cerebral perfusion pressure =MAP-ICP	continuous
Magnesium dose	Dose of magnesium infused (mg)	ordinal
Brain injury	Describes type of contusion: either SAH, SDH or multiple (complex)	categorical
Injury side	Side of the brain injured: either left, right or bilateral	categorical
GCS	Glasgow outcome scale: a measure of neurological impairment	categorical
Age	Patient age	continuous
Marshall Score	A score based on CT pathology	categorical
Surgery	A binary variable for surgery: binary due to multiple surgeries being common	binary
Magnesium protocol	Adherence to magnesium protocol: yes or no	binary
ICP protocol	Adherence to ICP protocol: yes or no	binary
Sedation protocol	Adherence to sedation protocol: yes or no	binary
Fluid protocol	Adherence to fluid replacement protocol: yes or no	binary

In considering a variable for inclusion in the model a p value of 0.15 or less was determined to be sufficient for the variable to be included in the adjusted model. If however, after modeling, the variable was not significant at a 0.05 level then it would be dropped from the final adjusted model. Each variable that was considered for inclusion was modeled separately with the magnesium infusion and time variables. After this process, the variables GCS, CPP, time FiO2 and magnesium infusion all had p values less than 0.15. All of these variables were placed into a model and the variable GCS was not significant at the 0.05 level and therefore was dropped from the model. Utilizing this stepwise model building approach, the variables included in the final model were time, FiO2, CPP, time, the time of magnesium infusion and the magnesium dose given (Figure 7). All of these variables were highly significant in the model (Table 10). First order interactions of these variables were not considered, because of the lack of biological interpretability.

$$E(Y_{ij} | b_i) = \beta_1 + \beta_2 \text{Mginfusion}_{ij} + \beta_3 \text{Time}_{ij} + \beta_4 \text{CPP}_{ij} + \beta_5 \text{FiO2}_{ij} + b_i + e_{ij}$$

Figure 7 The Equation for the Final Model of Licox Values

This equation shows the mean Licox response for the final adjusted model for the i^{th} individual at the j^{th} time adjusted for magnesium infusion, time, CPP and FiO2. b_i = random subject effects e_{ij} = error term β_1 = intercept parameter estimate; β_2 = magnesium infusion parameter estimate; β_3 = time parameter estimate; β_4 = CPP parameter estimate; β_5 = FiO2 parameter estimate.

The magnesium dose was modeled separately due to the variation in magnesium doses given to the patients and the relationship of the magnesium dose to the magnesium infusion variable. The same stepwise variable selection process used for the magnesium infusion model was done for the magnesium dose model. Only CPP and FiO2 levels were significant when modeled with magnesium dose and time after the dose. These variables were both significant in the model with the magnesium dose and time after dose variables, and therefore were included in the final model. The magnesium dose is an ordinal variable that was parameterized with a dose of zero grams as the reference level. Estimates for two, four, six and eight milligram doses are therefore parameterized in reference to periods when there was no magnesium given to the patient (Figure 8).

$$E(Y_{ij} | b_i) = \beta_1 + \beta_2 \text{Magdose}_{ij} + \beta_3 \text{Time}_{ij} + \beta_4 \text{CPP}_{ij} + \beta_5 \text{FiO2}_{ij} + b_i + e_{ij}$$

Figure 8 The Equation for the Final Model of Licox Values

This model was built using the final model for magnesium infusion. This equation shows the mean Licox response for the magnesium dose of the i^{th} individual at the j^{th} time adjusted for magnesium dose, time, CPP and FiO2. b_i = random subject effects e_{ij} = error term β_1 = intercept parameter estimate; β_2 = magnesium dose parameter estimate; β_3 = time parameter estimate; β_4 = CPP parameter estimate; β_5 = FiO2 parameter estimate.

Outliers occurred frequently in some patients in this study. Any value that is greater than the sum of the upper quartile and one and one half times the interquartile range, or less than

the lower quartile minus one and one half times the interquartile range is considered an outlier (Rosner 2000). In this data set the upper quartile of Licox values is 37mmHg and the lower quartile is 17 mmHg, giving an interquartile range of 20. Since values below the lower quartile range and negative and therefore impossible, Licox values above 68 mmHg will be considered outliers. The vast majority of outliers in this data set come from three patients who had prolonged periods of Licox levels above 68 mmHg. Therefore, in order to determine the influence outliers had on the modeling of this data, these three patients were removed from the data set and analysis was redone. These three patients received the same standard care as all other patients in this study, and there is no physiological reason to doubt the validity of these outliers. Therefore, these patients were not dropped completely from this study.

3.0 RESULTS

The focus of this study was to investigate the impact of magnesium infusion on a male population that had suffered a traumatic brain injury. The patients in this data set were white males between the ages of 18 and 51 (Table 3). These patients were mostly injured in motor vehicle accidents, requiring helicopter transport to PUH. They tended to have multiple contusions and hematomas of the brain, with some patients even presenting with the rare and commonly more lethal epidural hematomas (Table 4). Nine of the 17 patients had prior medical histories or multiple organ traumas that complicated their course of care. The presence of drugs and alcohol were confirmed by positive toxicology screenings on two of the patients in this data set (Table 5). Of the 17 patients in the data set, 9 had emergent brain surgery and 8 of these 9 patients underwent other surgical procedures due to the extent of their injuries (Table 6). The majority of patients were given magnesium within 24 hours of their injuries and five patients received multiple doses of magnesium (Table 7). Overall protocol adherence was excellent for all protocols except the magnesium protocol. The majority of patients were not dosed according to this protocol (Table 8). Five of the 17 patients in this study died, two patients were lost to follow-up after three months, and one patient refused further participation in the study (Table 9).

Table 3 Overall Demographic Breakdown of the Population

Variable	Categories	N	%
Failure of Protocol Compliance	Magnesium Replacement	12	54.5
	Admission	1	5.9
	ICP	2	11.8
	Sedation	0	0
	Fluid Replacement	6	35.3
Injury Type	SDH	6	35.3
	SAH	6	35.3
	Complex	5	29.4
Injury side	Right	4	23.5
	Left	5	29.4
	Bilateral	8	47.1
Mechanism of Injury	Car	8	47.1
	Motorcycle	5	29.4
	Other	4	23.5
Dose of Magnesium Given	2	3	13.6
	4	9	40.9
	6	5	22.7
	8	5	22.7
Age	18 to 30	11	64.7
	31 to 49	4	23.5
	50≤	2	11.8
GCS	3 to 5	7	41.2
	6 to 8	9	52.9
	Missing	1	5.9
Race	White	16	94.1
	African American	1	5.9
Prior Medical History			
Lung Disease	yes	1	5.9
	no	16	94.1
Surgery	yes	2	11.8
	no	15	88.2
Trauma	yes	1	5.9
	no	16	94.1
Psychiatric Disorder	yes	4	23.5
	no	13	76.5
Kidney Disease	yes	1	5.9
	no	16	94.1
Smoker	yes	3	17.6
	no	14	82.4

Table 4 Primary Head Injury Diagnosis and Marshall Score

UID	Primary Brain Injury	Marshall Score
467	right frontal contusion and SDH right parietal SAH	3
472	right frontal and temporal contusion bilateral SAH	2
474	left SDH	2
485	Bilateral SDH	3
518	left SDH	3
541	right temporal and bilateral frontal contusions with left SDH in frontoparietal region	2
547	left frontal and temporal contusions with SAH over same region	Not Scored
548	right parietal contusion with SAH	2
555	SAH over both lobes	Not Scored
575	Bilateral contusions with SDH	2
576	Bilateral SAH	2
582	Occipital and parietal SDH	Not Scored
586	Left frontal contusion with SAH	Not Scored
592	depressed left temporal fx with left frontoparietal contusion and temporal EDH	Not Scored
596	right SAH and right parietal SDH	Not Scored
616	extraaxial right frontal contusion (epidural) with various regions of SAH and SDH	Not Scored
621	bilateral frontal lobe contusions with left frontal epidural contusion and SAH	Not Scored

Shown here are the primary injury descriptions of the study population and Marshall Scores for each patient. SAH=subarachnoid hematoma; SDH=subdural hemotoma; EDH=epidural hemotoma. A Marshall score is a categorical score based on CT pathology that is related to outcome after trauma.

Table 5 Patient complications

UID	Preexisting and Post Injury Complications	Alcohol Use	Drugs Use
467	Diabetic	Nb	Nb
472	Moved after OR. Dr. Kassam saw pt. Delay of surgery to r/o death.	unknown	unknown
474	Ruptured spleen, L Wrist & shoulder Fx.	Yes	Nb
485	Pt. cooled from 39 to 37. GCS 4. Cooling Times unknown. Multiple facial fractures & pneumothorax.	unknown	unknown
518	None	unknown	unknown
541	None	unknown	unknown
547	None	unknown	Nb
548	SIADH	Nb	Nb
555	None	unknown	unknown
575	None	unknown	Nb
576	Post Surgical Meningitis	unknown	Nb
582	Massive brain swelling	Nb	Nb
586	Diabetic	unknown	Nb
592	None	unknown	unknown
596	None	unknown	unknown
616	Bilateral Hp Replacements	unknown	Nb
621	Bipolar	unknown	Yes

The above table contains information on patient complications, drug and alcohol screenings and emergency department medications. SIADH stands for Syndrome of Inappropriate Antidiuretic Hormone a condition that leads to hypertension through water retention by the kidneys.

Table 6 Surgeries Performed on the Patient Population

Uid	Surgical Procedures	Surgical Comment
467	Evacuated Hematoma	
467	Diagnostic Peritoneal Lavage	
467	Chest tube	
472	Lobectomy	Right Frontal
472	Craniofacial repair	Severl ENT procedures
472	Evacuated Hematoma	Craniotomy
472	Lobectomy	Right temporal
547	Evacuated Hematoma	
547	Remove bone flap	
555	Diagnostic Peritoneal Lavage	Clarion Hospital
555	Chest tube	pneumothorax
582	Lobectomy	Right Frontal and Temporal
582	Evacuated Hematoma	Temporal and Frontal
586	Elevate depressed skull fracture	
586	Craniofacial repair	
586	Laparotomy	
592	Evacuated Hematoma	
592	Evacuated Hematoma	
592	Lobectomy	left temporal / parietal
592	Elevate depressed skull fracture	
592	Craniofacial repair	
592	Laparotomy	open reinsertion of peg tube
595	Lobectomy	right frontotemporal
616	Chest tube	
616	Chest tube	
621	N.A.	

Shown here are the surgical procedures performed within the first 48 hours after injury for each patient.

Table 7 Magnesium dosing in the patient population.

UID	magnesium dose	TimeLag from Injury to Mg Dose	Initial Serum Mg
467	6	41	1.1
472	6	22	1
472	2	41	
474	4	20	1.2
474	4	27	
485	6	8.5	1.8
518	4	15	0.9
518	4	44.5	
541	4	30	1.3
547	6	4	1.1
548	4	27.5	1.6
555	2	11	1.1
575	8	16	1.2
576	8	15	1.1
582	8	11.5	1
586	8	8	1
592	4	29.5	1.5
596	4	18	1.2
596	4	42	
616	6	9	1.9
616	8	34	
621	2	15.5	1.2

General demographics for magnesium dosing in the patient population. This table shows the time to magnesium intervention and the dose of magnesium given in the study population. For some patients more than one dose of magnesium was given within the 48 hour period of observation. The serum mg variable is initial serum magnesium value for each patient.

Table 8 Protocol Adherence in the Study Population

UID	Dose	magnesium protocol	admission protocol	icp protocol	sedation protocol	fluid protocol
467	1	no:dose too low/time	yes	yes	yes	yes
472	1	no:dose too high	yes	yes	yes	yes
472	2	no:dose too low				
474	1	no:dose too low	no:elevated temperature	yes	yes	yes
474	2	no:dose too low				
485	1	no:dose too high	yes	yes	yes	yes
518	1	no:dose too low				
518	2	yes	yes	no	yes	yes
541	1	no:dose too low	yes	no: no mannitol given	yes	no: no levophed
547	1	no:dose too low	yes	yes	yes	yes
548	1	yes	yes	yes	yes	yes
555	1	no:dose too low	yes	yes	yes	no: no levophed
575	1	yes	yes	no: no mannitol given	yes	no: no levophed
576	1	yes	yes	no: no mannitol given	yes	no: no levophed
582		yes		yes	yes	yes
586	1	yes	yes	yes	yes	yes
592	1	yes	yes	yes	yes	yes
596	1	no:dose too low	yes	yes	yes	yes
596	2	no:dose too low				
616	1	no:dose too low	yes	yes	yes	yes
616	2	yes				
621	1	no:dose too low	no: hypertension	yes	yes	yes

Protocol adherence in the study population. Patients were determined to not be in protocol adherence if they had not been given indicated medications, interventions, or correct dosages of medications the protocol indicate should be given for the patients given condition.

Table 9 GOS Scores for Patient Population

UID	3 Month GOS	6 Month GOS	12 Month GOS	24 Month GOS	Days till Death
467	1	1	1	1	3
472	1	1	1	1	8
474	3	90	90	90	
485	1	1	1	1	3
518	3	4	4	90	
541	5	5	5	90	
547	4	3	3	90	
548	4	4	4	5	
555	2	3	3	90	
575	3	92	5	5	
576	1	1	1	1	12
582	1	1	1	1	3
586	3	3	3	90	
592	90	90	90	90	
596	4	4	90	90	
616	5	5	5	90	
621	96	96	96	96	

GOS scores for the population. Patient outcomes at 3, 6, 12, and 24 months. Codes are as follows 90 = patient lost to follow up; 92 = unable to assess; 96 = patient refused continued participation.

3.1 DATA ANALYSIS

The data were first modeled by constructing the baseline model with the independent variables time and magnesium infusion time. The residuals were not normal in the data set for all models due to a tendency for Licox values to cluster in the 20 to 30 mmHg range (Figure 9 and Figure 10). The model showed a very slight decrease in Licox values when a magnesium infusion occurred. Modeling showed that Licox was increased by 3.935 mmHg during periods when no magnesium infusions were occurring (Figure 11, Table 10). This decrease is not clinically significant, as Licox values can fluctuate by as much as five millimeters of mercury per minute or more during the normal course of a patient's stay in the NICU.

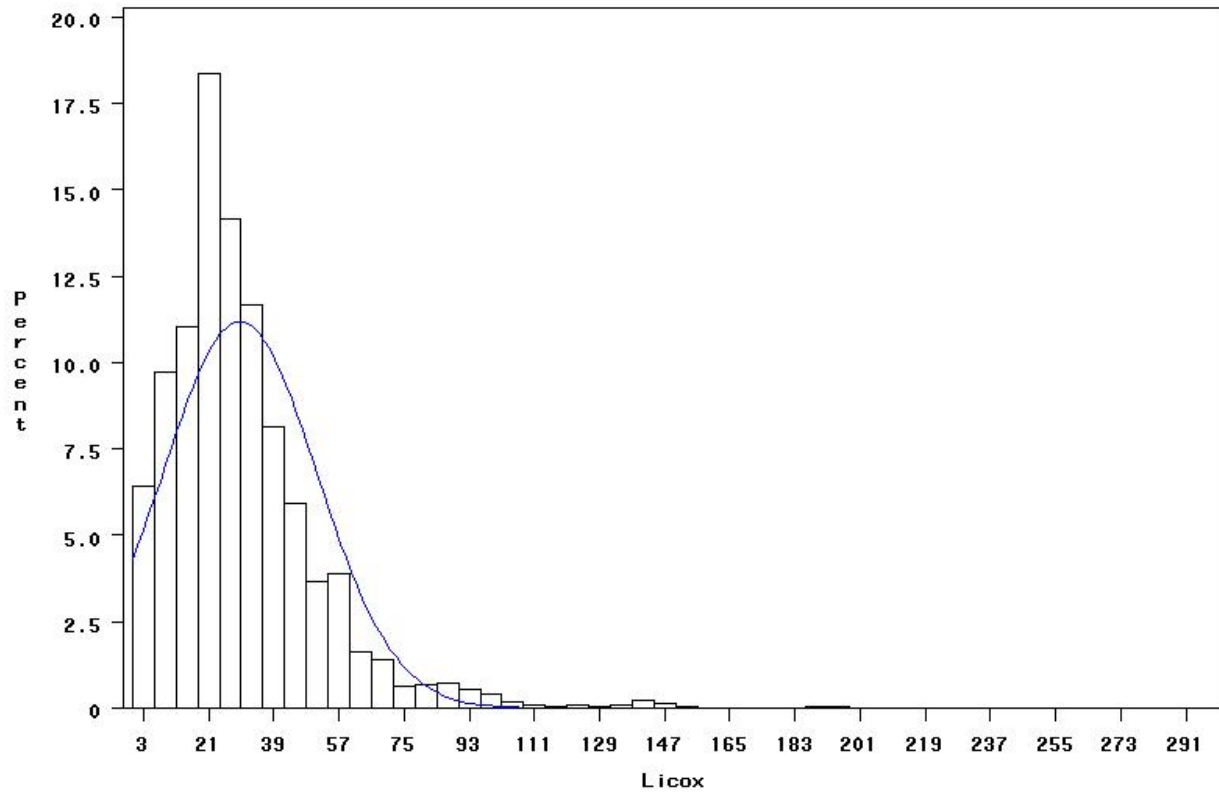


Figure 9 Histogram of Licox Values Showing Skewness and Extreme Kurtosis.

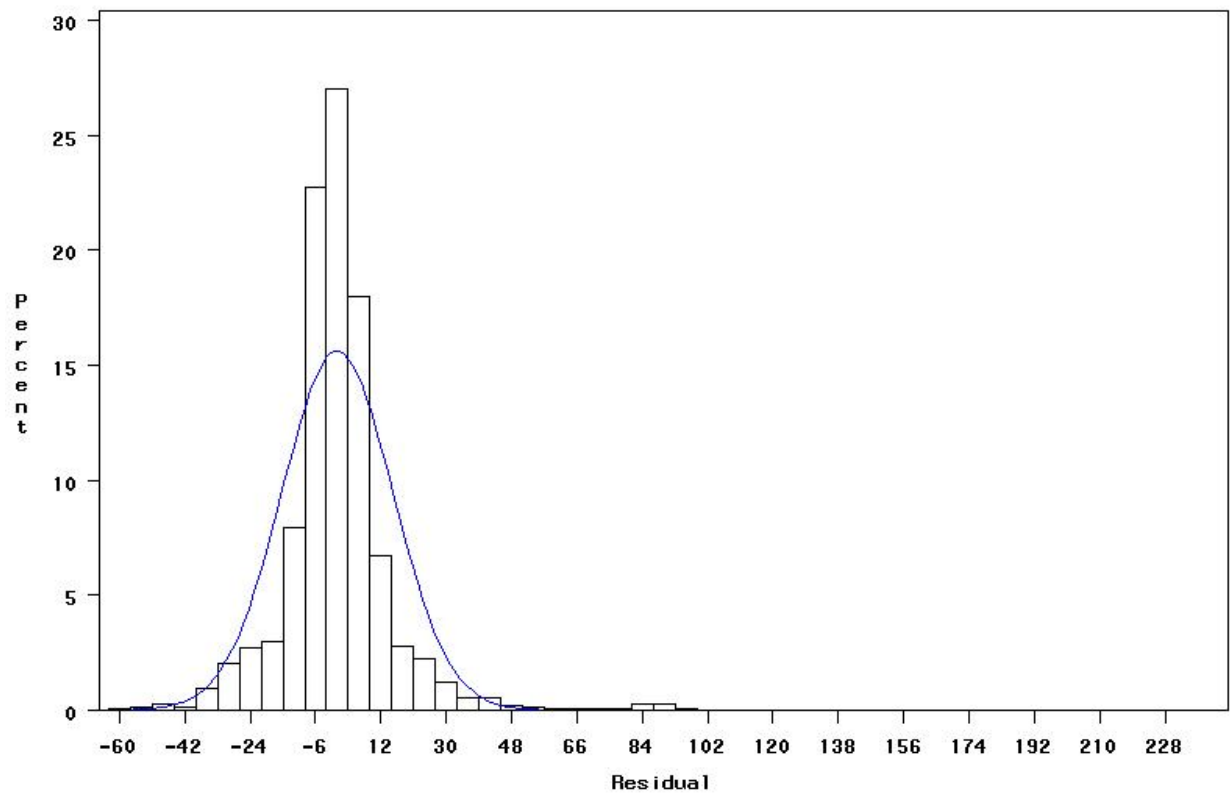


Figure 10 Histogram of residuals for the final model.

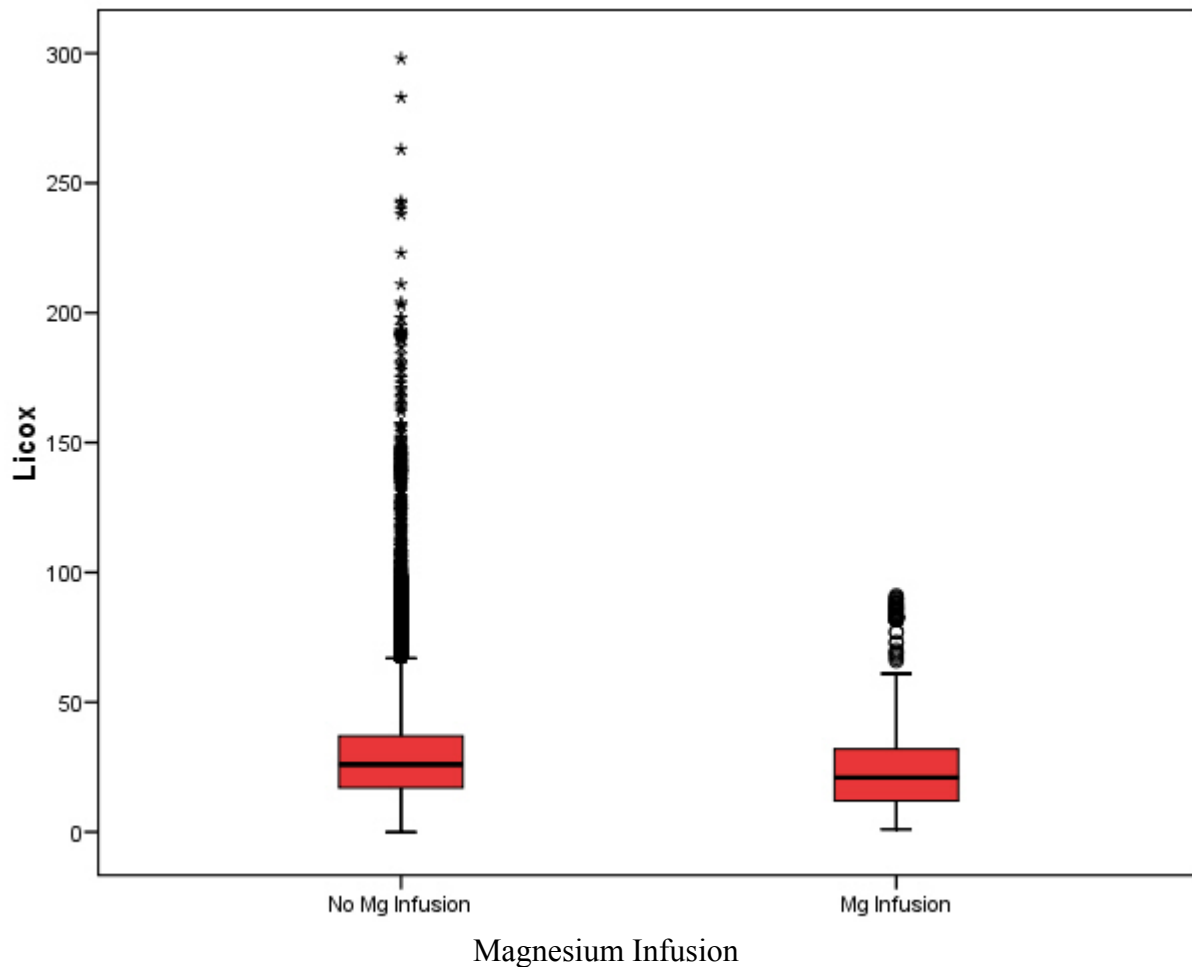


Figure 11 Boxplot of Licox Values by Magnesium Infusion Variable

The parameter estimate for the time after a magnesium infusion is extremely small. However, it is positive, suggesting that as time after an infusion progresses, Licox values increase (Table 10). Since the time variable is constructed as a minute measurement, it could have a significant impact on Licox values as the patient progresses over the two day period of this study. The fact that the parameter estimate is positive indicates that magnesium infusion are associated with increases in brain tissue oxygen over time, most likely due to vasodilation of the vasculature.

Table 10 Results of Modeling the Licox Data by Magnesium Infusion

Variable	Beta	Standard Error	P Value	Lower CL	Upper CL	L S Means
Base Model						
intercept	24.309	3.151	<0.0001	17.756	30.862	
Mginfusion 0	3.935	0.282	<0.0001	3.383	4.488	28.616
Mginfusion 1						24.681
Time (minutes after infusion)	0.001	0.0001	<0.0001	0.0005	0.001	
Autoregressive Covariance	216.92	66.948	0.0006			
Final Model						
intercept	12.015	3.251	.00014	5.246	18.785	
Mginfusion 0	2.812	0.367	<0.0001	2.094	3.532	27.698
Mginfusion 1						24.886
Time (minutes after infusion)	0.001	0.001	<0.0001	0.0005	0.001	
FiO2	-0.039	0.009	<0.0001	-.0559	-0.022	
CPP	0.200	0.007	<0.0001	0.185	0.214	
Autoregressive Covariance	214.57	66.958	0.0007			
Final Model (Outlier Patients Removed)						
intercept	8.372	2.892	0.01	2.296	14.448	
Mginfusion 0	0.045	0.257	0.861	-0.459	0.549	23.191
Mginfusion 1						23.146
Time (minutes after infusion)	0.0001	0.0001	0.441	-0.0001	0.0003	
FiO2	0.020	0.007	0.004	0.007	0.034	
CPP	0.191	0.005	<0.001	0.181	0.201	
Autoregressive Covariance	150.31	50.68	0.0015			

Table 11 Results of Modeling the Licox Data by Magnesium Dosage

Variable	Beta	Std Error	P Value	Lower CL	UpperCL	LS Means
Base Model						
intercept	28.105	3.187	<0.001	21.478	34.731	
Magdose=0						28.365
Magdose=2	4.956	1.152	<0.001	2.699	7.214	33.321
Magdose=4	3.617	0.479	<0.001	2.679	4.555	31.982
Magdose=6	-10.912	0.541	<0.001	-11.972	-9.853	17.453
Magdose=8	-7.500	0.470	<0.001	-8.417	-6.575	20.869
Time (minutes after infusion)	0.0005	0.0001	<0.001	0.0003	0.0007	
Autoregressive Covariance	223.11	68.922	0.0006			
Final Model						
intercept	15..301	3.305	0.0001	8.429	22.174	
Magdose=0						26.879
Magdose=2	8.980	1.352	<0.001	6.330	11.630	35.859
Magdose=4	8.500	0.665	<0.001	7.197	9.802	35.378
Magdose=6	-7.804	0.770	<0.001	-9.313	-6.295	19.075
Magdose=8	-9.772	0.541	<0.001	-10.832	-8.713	17.106
Time (minutes after infusion)	0.0004	0.0002	0.0296	0.00004	0.0007	
FiO2	-0.045	0.009	<0.001	-0.062	-0.027	
CPP	0.191	0.007	<0.001	0.176	0.206	
Autoregressive Covariance	223.68	69.680	0.0007			
Final Model (Outlier Patients Removed)						
intercept	7.605	3.101	0.025	1.089	14.121	
Magdose=0						22.986
Magdose=2	-9.614	1.206	<0.001	-11.978	-7.251	13.372
Magdose=4	8.189	0.419	<0.001	7.367	9.011	31.175
Magdose=6	-9.321	0.551	<0.001	-10.401	-8.241	13.665
Magdose=8	-1.913	0.386	<0.001	-2.670	-1.157	21.073
Time (minutes after infusion)	-0.0003	0.0001	0.01	-0.001	-0.0001	
FiO2	0.045	0.007	<0.001	0.0307	0.058	
CPP	0.181	0.005	<0.001	0.171	0.191	
Autoregressive Covariance	175.36	59.0337	0.0015			

The parameter estimate for magnesium infusions in the base model was 3.935. In the adjusted model, the value for the parameter estimate dropped to 2.812. This is once again a clinically insignificant drop in Licox values. It is also surprising that the adjusting for FiO₂ and CPP levels did not have a greater influence on the parameter estimate for magnesium infusions. There is a slight decrease in CPP levels during a magnesium infusion. This is consistent with the known properties of magnesium as a vasodilator (Figure 12). The fact that both Licox and CPP levels show a mild and not a profound decrease during a magnesium infusion supports the theory that magnesium is dilating smaller blood vessels.

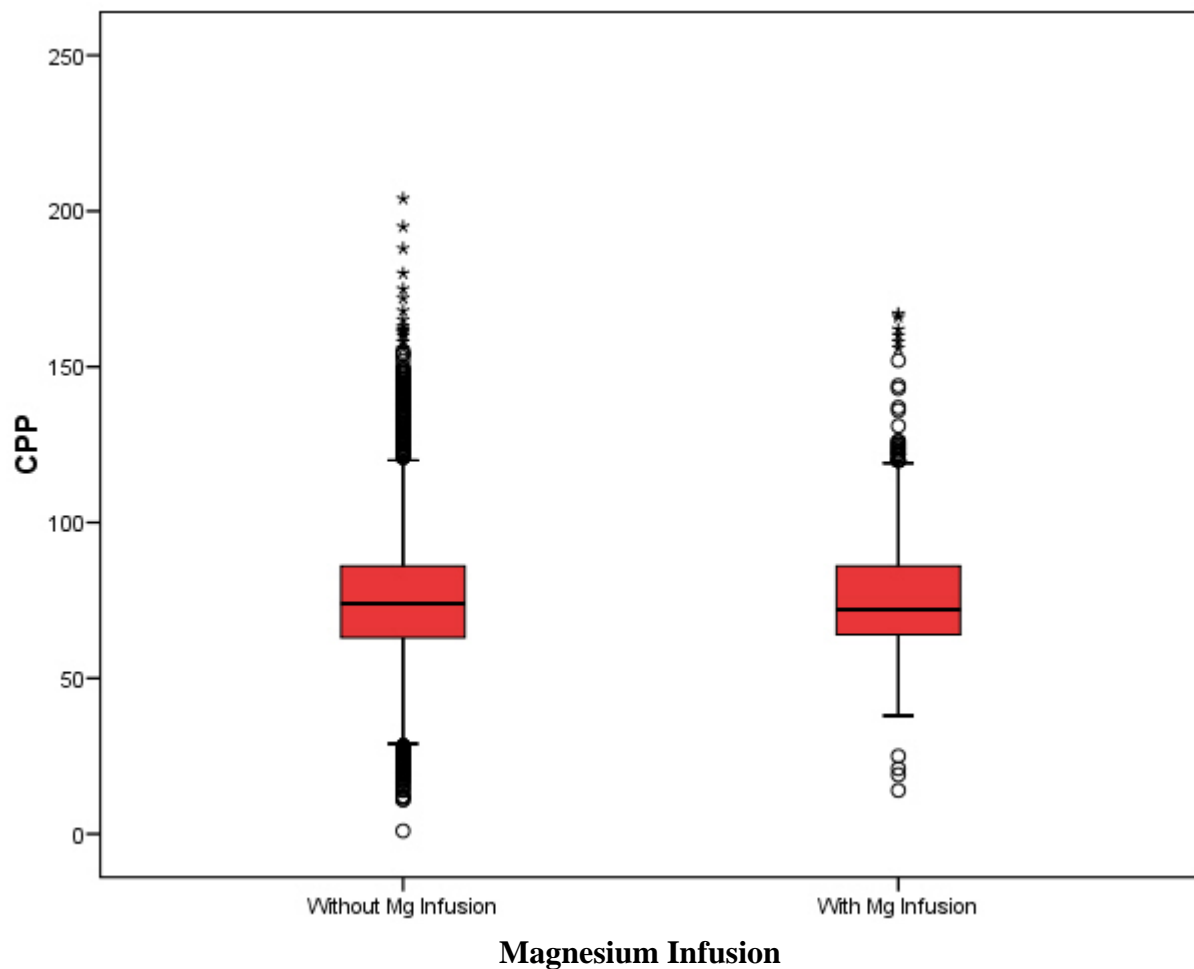


Figure 12 Boxplot of CPP values by Magnesium Infusion Status.

The time after magnesium infusions variable was not affected by adjusting for either FiO2 or CPP in the final model. Both the base and final adjusted model show that Licox values increase as the time after a magnesium infusion progresses. There was a positive correlation with time and CPP levels during both periods of magnesium infusion as well as periods without an infusion (Figure 13 and 14). Since CPP is a measure of large vessel perfusion, the increase in CPP over time indicates that the large blood vessels of the brain are not dilating in response to magnesium infusions.

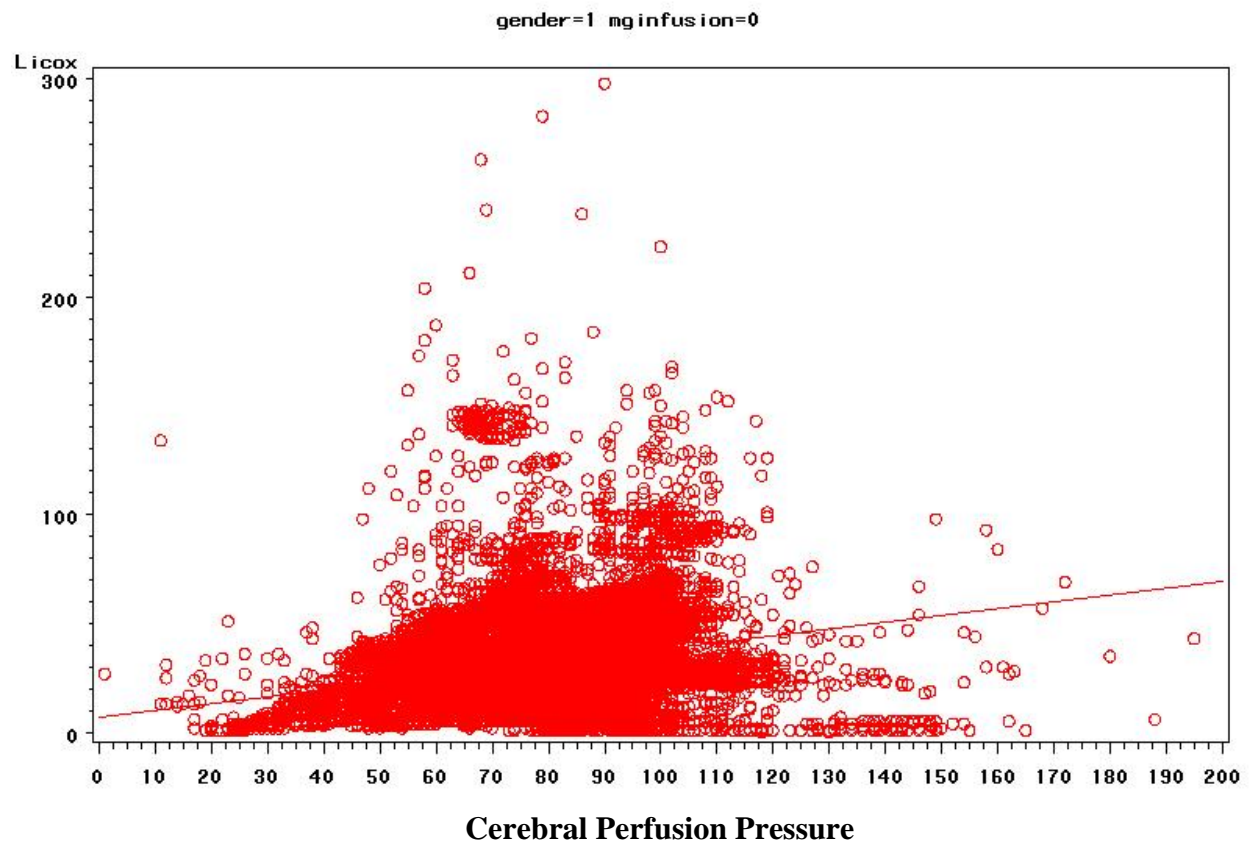


Figure 13 Scatter Plot of Licox Values Versus CPP Values During Periods Without Magnesium Infusions.

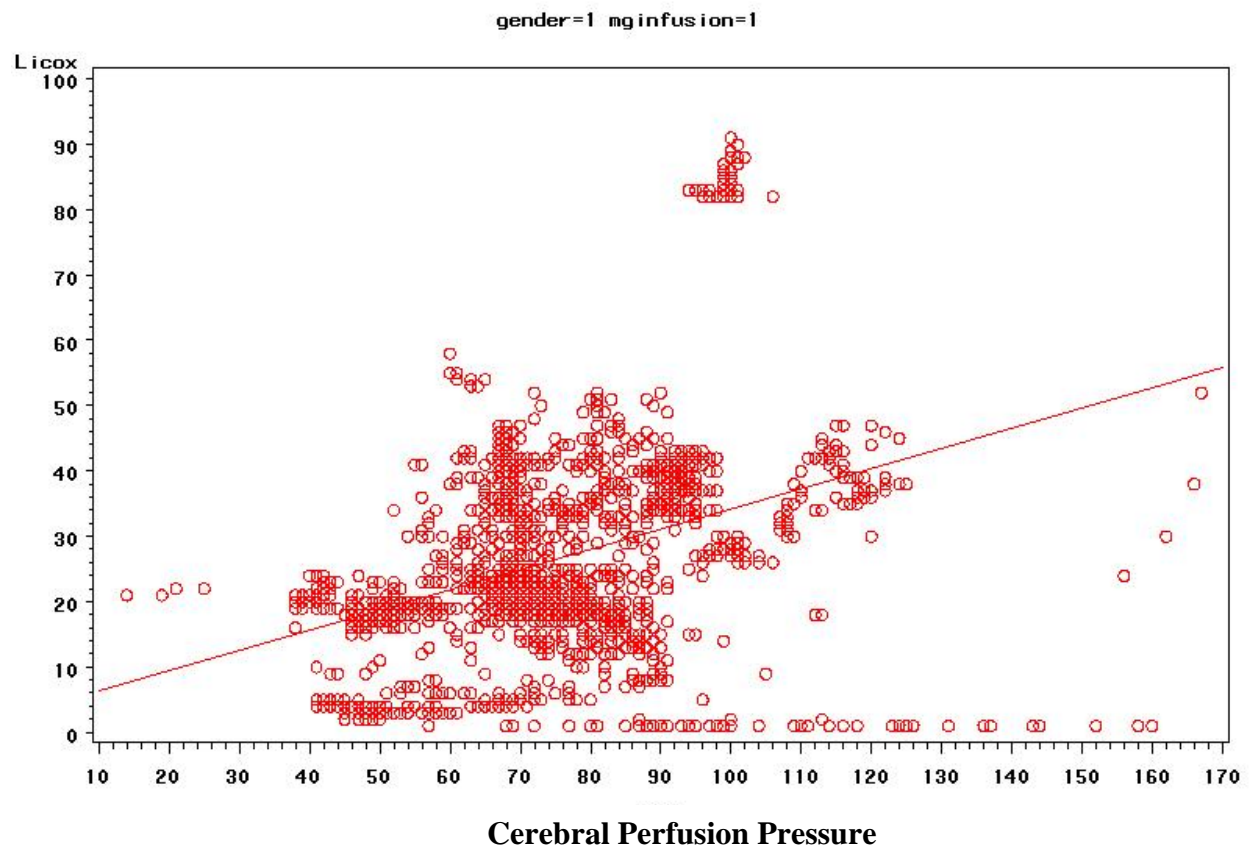


Figure 14 Scatter Plot of Licox Values Versus CPP Values During Magnesium Infusions

A base model was fit for the magnesium dose given to each patient. In this model patients with doses of six or eight grams showed the largest response to magnesium. The parameter estimates for the six and eight gram dosing groups were -10.912 and -7.500 respectively. This is a clinically significant drop in Licox values, given that the normal range is 20 to 30 mmHg (Table 11). The large decreases in Licox values in the six and eight gram dosing groups indicates that there is an optimal dose for magnesium. If magnesium is given to the patient is in excess of this optimal dose, it could induce tissue hypoxia.

The parameter estimate for time after magnesium infusion was again positive, but of smaller magnitude in this model compared to the model for magnesium infusion. The time after magnesium infusion variable was fit in the same manner as in the magnesium infusion model as a continuous variable fit for every minute of observation on the unit. The smaller parameter estimate for the time after a magnesium infusion in this model compared to the magnesium infusion model is due to the separate modeling of the patients by dose. Decreases in Licox values in the six and eight gram dosing groups are negatively influencing the parameterization of the time after magnesium infusion variable.

In the final adjusted model there were clinically relevant changes in tissue oxygenation across all dosing groups. The pattern of lower Licox values in those patients given six or eight gram doses of magnesium were also seen in the final adjusted model. Parameter estimates for the six and eight gram dosing groups were -7.804 and -9.772 respectively (Table 11). In those patients receiving two and four gram doses, the parameter estimates were 8.980 and 8.500 respectively. These results indicate the impact magnesium has on vasodilation, and therefore brain tissue oxygen levels are dose dependent (Figure 15). This model supports the results of the base model, which also showed a dose dependent effect. These results show that lower doses of magnesium merit consideration as a treatment for brain tissue hypoxia.

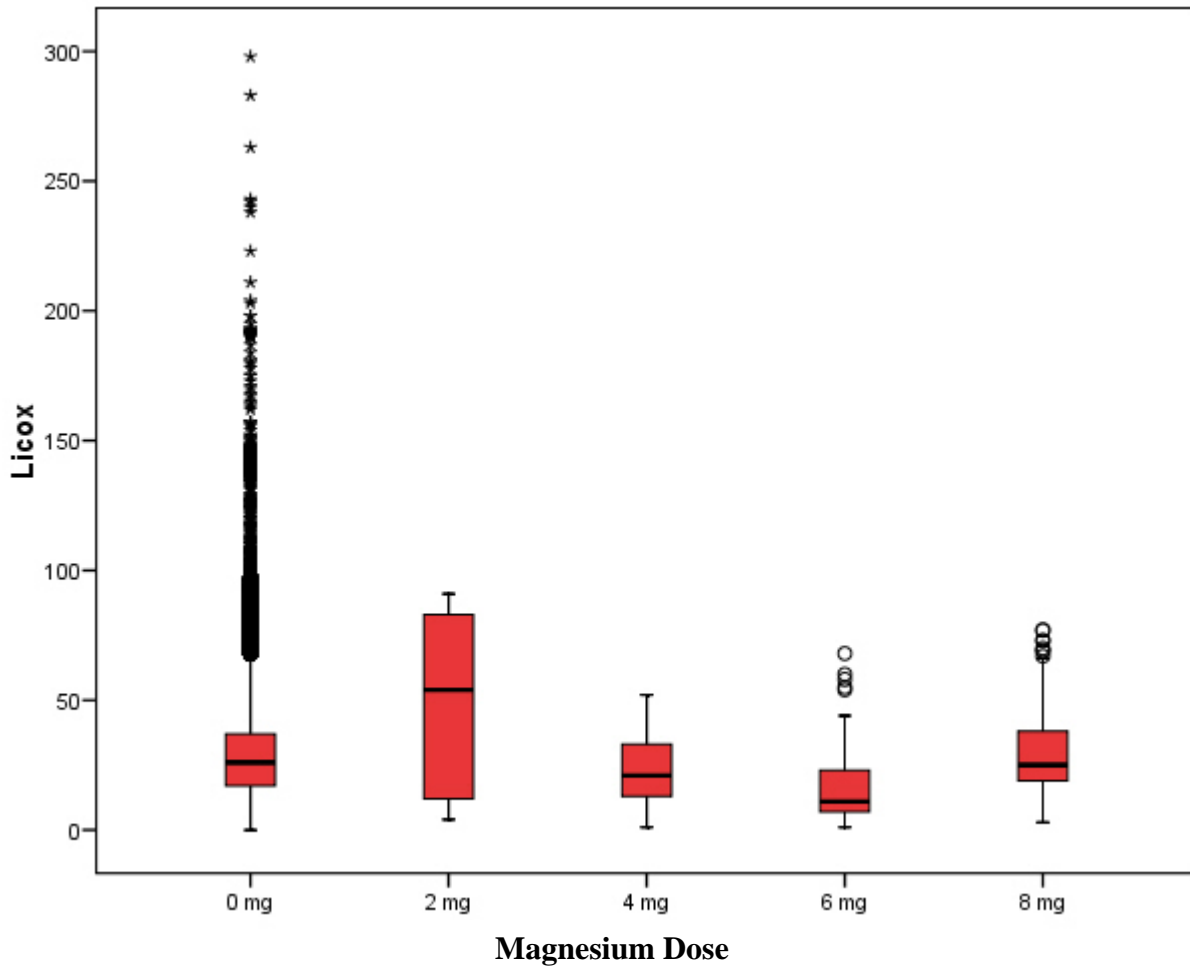


Figure 15 Boxplot of Licox Values by Dose of Magnesium Infused.

The parameter estimate for the time after magnesium infusions was relatively unchanged in the final model. The parameter estimate went from 0.0005 to 0.0004 in the final model. As in the final model for magnesium infusion, adjusting for FiO₂ and CPP levels has almost no effect on the time after magnesium infusions. Overall however, there is still an increase in Licox values after a magnesium infusion. It is possible given how magnesium is infused in this patient population, that there is an early decrease in Licox values in the six and eight gram dosing groups followed eventually by a more gradual recovery of tissue oxygen levels.

There were three patients in this data set that had prolonged periods of outlying Licox values. These patients had an influence on the parameterization of both the magnesium infusion and dose models. In the magnesium infusion model with these patients removed there was almost no difference in the Licox values with or without magnesium infusions. The magnitude of the parameter estimate for time after an infusion was greatly reduced, but still positive. In the magnesium dose model without these patients there is still an indication that there is an optimal dose for a magnesium infusion after head injury. This parameter estimate for the two gram dosing group was profoundly altered, but this was the smallest dosing group and the removal of patients from this group has a larger effect on the parameter estimate. The parameter estimate for time after magnesium infusions in this model was negative, indicating that the prolonged periods of outliers in the patients removed occurred mainly after magnesium infusions.

4.0 DISCUSSION

There was little variation in Licox values during a magnesium infusion. The decreases in Licox values during a magnesium infusion were not clinically relevant in any analysis of the data set. Since the magnesium is being infused through a central subclavian line, the results of this study indicate a lack of effect by magnesium on large blood vessel vasodilation. This is consistent with clinical evidence of magnesium use in preeclamptic women (Belfort et al. 1999). If large blood vessels were being dilated due to magnesium, there should be a profound effect on the oxygen levels reaching the brain tissue. Not only was this not seen, but when outliers were removed from the data, there was almost no change in Licox values due to a magnesium infusion. There was no dramatic reduction in Licox values in any of the models of magnesium infusion. So it is safe to conclude that large blood vessels were not either at the point of magnesium entry into the body or at vessels distal to the point of infusion.

In the magnesium dose models there appeared to be a dose dependent change in Licox values. In the base and final adjusted models, patients receiving six and eight gram doses had large decreases in their Licox values during a magnesium infusion. Also, the two and four dose groups had significant improvements in their Licox values in the adjusted model. These results indicate that lower doses of magnesium are optimal in this patient population. This was especially true for the four gram dose group, which had a consistent increase in Licox values across all models. Therefore, low doses of magnesium may be therapeutic for brain tissue

hypoxia. Further investigation of these results is warranted, but is beyond the scope of this study, as it would involve the use of more sophisticated time series analysis models in order to determine the initiation and duration of the effect.

The magnitude of the time after magnesium infusion variable was relatively unchanged across both the magnesium infusion and magnesium dose models. The most significant change was seen across the magnesium infusion and magnesium dose models. This is due the separation of patients by dosing category and the subsequent drop in Licox values at higher dosing levels. The fact that oxygen levels increased in both models with time shows that magnesium is having a prolonged vasodilation effect on this population.

Licox values increase with CPP in both the magnesium infusion and dose models. However, there are periods when the patient has adequate perfusion yet poor oxygenation of the brain tissue, as well as periods when patients have adequate oxygenation during periods of poor tissue perfusion. These apparently anomalous results may represent periods of loss of cerebral autoregulation or possibly periods of cortical spreading depression (Werner and Engelhard 2007; Strong et al. 2007). Both loss of autoregulation and cortical spreading depression are likely to occur in these patients, and further research is necessary to determine how these events impact Licox values. The parameter estimates for CPP are not large, mostly due to the fact that it is a continuous variable in the model. However, large changes in the CPP levels can and often do occur in these patients and these fluctuations would have enormous implications for tissue oxygenation based on these models.

Licox values decreased slightly when the FiO₂ levels were raised in both of the final adjusted models. FiO₂ was fit as a continuous variable and therefore the parameter estimate is small. It was surprising that the effect that was seen was negative in the final adjusted model.

This indicates that magnesium is increasing oxygen delivery to the tissue despite a decrease in the inspired oxygen. Therefore, increases in FiO_2 during a magnesium infusion may not be warranted, for especially those patients receiving a four gram dose of magnesium, which may lead to an over abundance of oxygen in the tissue. These luxuriant oxygen levels can be potentially harmful. It could lead to oxidative cell damage and even death as oxygen is radicalized by aberrant cellular metabolism. The small negative effect of FiO_2 may have another possible cause, as it is not uncommon for there to be no response or a lag in response by the Licox probe to changes in FiO_2 levels. It is not clear what the exact cause of this lagging or absent response is, but it is likely related to damage to the vasculature of the brain itself. Periods of irregular blood flow are common after brain injuries due to a phenomenon called vasospasm (Oertel et al. 2005). These uncontrolled contractions of the brain vasculature influence the delivery of blood to all regions of the brain (Oertel et al. 2005). Since there is an inflammatory reaction in the vasculature associated with vasospasm, it is not inconceivable that entire regions of the brain are under perfused or even deprived of blood during vasospasm (Oertel et al. 2005). This of course would be more likely to occur in patients who have multiple brain injuries as well as those patients with a poor neurological prognosis. The relationship between Licox and FiO_2 could also indicate a surprising preservation of vasculature carbon dioxide reactivity by this patient population (Werner and Engelhard 2007). The fact that there are more outliers in Licox values at the lower levels of FiO_2 support this theory (Figure 12). Since loss of carbon dioxide reactivity occurs early after trauma it is likely to occur during the time period of this study (Werner and Engelhard 2007). Carbon dioxide reactivity is likely to have a significant effect on this data, as it would influence Licox values especially for those patients having a poor neurological outcome (Werner and Engelhard 2007).

The outliers in the Licox data were a particular problem in this data set. The majority of outliers came from three of the patients in the data set, patients 547, 586 and 621. Patient 621 refused further participation in the study so the neurological outcome for this patient is unknown. Patient 586 had a GOS of 3 which did not change at any of the follow-up appointments for neurological testing. Patient 547 a good three month outcome and then later deteriorated to a poor outcome. Removing these patients had significant impact on both models. The parameterization of the magnesium infusion, magnesium dose, time after a magnesium infusion and FiO2 variables was profoundly influenced by the presence of these patients. The cause of the elevated oxygen levels in these patients is undetermined. Spikes in Licox values occurred after day one for patient 586 and intermittently through both days for patients 621 and 547. The true cause of these spikes in Licox may become evident in subsequent patients, as a protocol is now in place to monitor for cortical spreading depression. These patients are obviously exerting an influence on the conclusion of this study. However, there is no reason to drop the patients, since there is no reason to doubt the validity of their data.

The results of clinical trials in both stroke and head injury show that magnesium supplementation increases patient mortality and morbidity (Temkin et al. 2007; Lees et al. 2004). Patients who do survive a brain injury may never fully recover, and those who do often require intensive physical and mental rehabilitation. This long term process places a great financial burden on the health care system, and a great social burden on communities due to the loss of productive life years that brain injury patients' experience. The public health significance of this study is that by elucidating how magnesium contributes to poor outcomes after head injury mortality and morbidity after brain injuries may be reduced.

5.0 CONCLUSIONS

Overall, there was little change in Licox values in the magnesium infusion model when adjusting for time after magnesium infusions, CPP, and FiO₂. The magnesium dose model seems to indicate that there is an optimal dose for magnesium in head injury patients. Both models provide evidence that serum magnesium dosing is not causing anoxia after head injury. In fact, there is a Those patients that are extremely sensitive to the dosing are at greater risk for hypoxia, which will further endanger the brain tissue.

There was very little movement in the GOS values after the 3 month outcome test. Only six patients, had a change in either direction over the 6, 12 or 24 month outcome tests. Of these six patients one regressed from a 4 to a 3 and the rest improved only one point on the scale. This is a very common result. Those patients surviving the injury can improve neurologically through the intensive rehabilitation processes they undergo, but change is often not dramatic. This lack of improvement is the main reason why the prevention of secondary injuries to the brain is so critical after closed head trauma. The very nature of the neural environment places brain cells in a very precarious position, and trauma to the brain can have necrotic effects on brain tissue that is distal to the injury core.

The failures of the clinical trials with magnesium should not be ignored. Identifying and understanding the mechanism by which magnesium increased mortality in brain injury trials might elucidate ways to decrease mortality and improve outcome after head injury. The results

of this study show that magnesium can influence cerebral physiology, and therefore impact neurological outcome in head injury patients. Future studies of the effects of magnesium should include a larger and more diverse patient population, as it is likely that the results of this study would have been different if a sufficient female population was available. Also, future research using intensive repeated measures analysis should incorporate more dynamic statistical modeling. More advanced time lagged and time series models may fit this data better and therefore clarify the relationship between magnesium and tissue oxygenation.

APPENDIX A: TRAUMATIC BRAIN INJURY PROTOCOLS



PHYSICIAN ORDER SET

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NURSE TO ADMINISTER THE GENERIC OR CHEMICAL EQUIVALENT WHEN
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Account Number:

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Severe Traumatic Brain Injury Admission Protocol -- Physician Order Set

Admit to(Unit): _____ Attending Physician: _____
Diagnosis: **Severe traumatic brain injury** Condition: _____
Allergies: _____

Check All Orders that Apply with a ☒ & All Handwritten Orders Should be **BLOCK PRINTED** for Clarity

Communication Orders

- ☒ Notify Neurosurgery on-call for any of the following:
- | | | |
|---|--|--|
| <input type="checkbox"/> If core temperature > 38.3° C. | <input type="checkbox"/> pCO ₂ < 33 or > 37 | <input type="checkbox"/> ICP > 20 mm Hg |
| <input type="checkbox"/> Hct < 28 | <input type="checkbox"/> CPP < 60 mm Hg | <input type="checkbox"/> MAP < 65 or > 110 mm Hg |
- ☒ Contact Critical Care Medicine for insertion of the following catheters:
- | | |
|---------------------------------------|--|
| <input type="checkbox"/> Central line | <input type="checkbox"/> Arterial line |
|---------------------------------------|--|

Vital Signs

- ☒ Record vital signs, including Licox PbtO₂, brain temperature, local blood flow, Bispectral Index (BIS), end tidal CO₂ (EtCO₂), and rectal temperature every 1 hr x 5 days

Activity

- ☒ Elevate head of bed 30°

Patient Care

- ☒ Maintain core temperature between 36.5° C. - 37.5° C. with cooling blanket and ice lavage prn
- ☒ External Ventricular Drainage (EVD) open at 10 cm above midbrain, close every 1 hour and record ICP reading following 5 minutes equilibration; notify Neurosurgery if ICP > 20 mm Hg
- ☒ Ventilatory: Maintain arterial pCO₂ = 33-37; adjust respiratory rate by 2 breaths/minute hourly prn to achieve goal
- ☒ Obtain doppler exam of lower extremities every 7 days while in ICU

Continuous Infusions

- ☒ 0.9% Sodium Chloride with KCl 20 mEq/L at 100 ml/hour ☒ All diluents in 0.9% Sodium Chloride solution
- ☒ Serum Sodium Goal = _____ mEq
- If current sodium is < goal listed above, change IV fluids to 2% sodium chloride (50% acetate: 50% chloride) + KCl 20 mEq/L at 100 ml/hour
- If CPP < 60 mm Hg, or MAP < 65 mm Hg, follow fluid management orders per **Severe TBI: Fluid Resuscitation Protocol**

Medications

- ☒ Propofol 20 mcg/kg/minute - IV infusion, then titrate per **Severe Traumatic Brain Injury Sedation Protocol**
- ☒ Fentanyl 50 mcg/hour IV infusion, may titrate prn, per **Severe Traumatic Brain Injury Sedation Protocol**
- ☒ Phenytoin (**Dilantin**) 1 gram IV loading dose, if not previously given
- ☒ Phenytoin (**Dilantin**) 100 mg IV every 8 hours Next dose due (military time): _____
- ☒ Enoxaparin 30 mg subq q12 hrs. Start 48 hrs after admission, notify Neurosurgery prior to 1st dose being administered DO NOT SUBSTITUTE
- ☒ Acetaminophen 650 mg NG/PR every 4 hours prn - core temperature > 38.0° C
- ☐ Ampicillin/sulbactam (**Unasyn**) 3 grams IV every 6 hrs X 16 doses. If penicillin allergy, call CCM for alternative.

(BLOCK Print Name)

(Signature)

Date / Time: _____ Pager # _____



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Severe Traumatic Brain Injury Admission Protocol -- Physician Order Set

Labs

- ☒ Serum EtOH level upon admission, if not done in E.D.
- ☒ Urine Toxicology Screen upon admission, if not done in E.D.
- ☐ Pregnancy test upon admission, if not done in E.D.
- ☒ Serum sodium every 6 hours
- ☒ Arterial blood gas every 6 hours and one hour following ventilatory adjustment
- ☒ CSF sampling q 4 hours x 24 hours, then q 6 hours x 4 days, after consent is obtained

Radiology

- ☐ CT Scan of the head with perfusion the next morning following admission (reason): _____
If contrast allergy, substitute a CT scan of the head, no contrast

Consult the following services for TBI evaluation:

- ☒ Physical Therapy and Occupational Therapy
- ☒ Social Services
- ☒ Rehabilitation Medicine

Additional Orders Should be BLOCK PRINTED for Clarity

The following abbreviations are disallowed: u (unit), MS and MSO4 (morphine), MgSO4 (magnesium sulfate), µg (microgram), QD (daily),
QOD (every other day), IU, (International Units), TIV (three times weekly) and BT (bedtime).

Other Orders	Medication Orders

Safe Prescribing Practices: Verify all orders by reading the order back to the prescriber. Do not use zeros following a decimal point. Use a zero
before a decimal point. Order IV medications by dose per time (e.g., mg/hr). Order levothyroxine in "mcg" (not "mg") doses.

(BLOCK Print Name)

(Signature)

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Figure 16A Admission Protocol



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Severe Traumatic Brain Injury: Intracranial Hypertension -- Physician Order Set

ICP Maintenance: (Normal Pressure < 20)

Step

1. ICP > 20

- Continuous CSF drainage via EVD at 10 cm above midbrain, per initial Severe Traumatic Brain Injury Admission Protocol
- Verify adequate sedation/analgesia per initial Severe Traumatic Brain Injury Sedation Protocol

2. ICP consistently > 25, after step 1

If closed ICP reading is 25-29 mm Hg after 2 consecutive hourly readings, or > 30 mm Hg for 1 hourly reading, notify Neurosurgery and proceed with Steps 2a-b.

Obtain orders from Neurosurgery for proceeding with steps 2c-d and step 3

- STAT CT head scan to rule out mass lesion
- Mannitol 0.5 gms/kg IV x1, while hypertonic Sodium Chloride being prepared, repeat x1 if no response in ICP
 - Check serum osmolality q 6 hours
 - Hold Mannitol for serum osmolality > 315 mOsm/kg

- ☐ c. Discontinue maintenance fluid and begin hypertonic sodium chloride [_____ %] (50% chloride: 50% acetate) with KCl 20 mEq/L at 100 ml/hr

- Serum Na⁺ Goal 150-155 mEq
- Check serum Na⁺ q 6 hours
- If serum Na⁺ > 155 mEq, change to 0.9% sodium chloride with KCl 20 mEq/L at 100 ml/hr

- ☐ d. Decrease arterial pCO₂ (to Goal to 29-31)

- Increase ventilatory rate to reach pCO₂ Goal
- Wean back to pCO₂ = 33-37, once ICP < 20 mm Hg

3. ICP consistently > 25 after step 2

If closed ICP reading is 25-29 mm Hg after 2 consecutive hourly readings, or > 30 mm Hg for 1 hourly reading, after steps 2a-d have been performed, notify Neurosurgery for additional orders (i.e. pentobarbital administration).

- ☐ Begin pentobarbital administration

- Pentobarbital 10 mg/kg IV - loading dose
- Continuous EEG monitoring
- ☐ Pentobarbital 1 mg/kg/hour IV - for 15 minutes q hour as maintenance dose ■ Titrate for burst suppression of 50%
☐ Pentobarbital 2 mg/kg/hour IV - for 15 minutes q hour as maintenance dose ■ Titrate for burst suppression of 50%
- Maintain Cerebral Perfusion Pressure > 60 mmHg during barbiturate use.
- Titrate pressor for CPP > 60 mm Hg as needed:
☐ Norepinephrine (Levophed) 0.1 mcg/kg/minute IV, titrate for effect

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(Signature)

Date / Time:

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0031-01-U

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SEVERE TBI ORDERS
ICP MAINTENANCE PROTOCOL

Protocol Goals: The main goals of this protocol are to provide a standardized approach to ICP management in patients with severe TBI, and to provide the nurse with guidance to the next level of control for elevated intracranial pressure.

Protocol Triggers: The patient will be eligible for ICP management by protocol if they develop intracranial hypertension (ICP > 20 mmHg). ICP reading must be obtained in a 'closed to the head' stopcock position, after a 5 minute equilibration period.

Protocol Details:

- 1 The External Ventricular Drainage (EVD) system is to be maintained open at 10 cm above midbrain, for continuous CSF drainage. Every hour, close EVD stopcock to the head and record ICP reading following a 5 minute equilibration. Mark all other ICP readings as 'open' in the Emtex system.
- 2 If closed ICP reading is > 20 mm Hg verify adequate sedation/analgesia per **Severe Traumatic Brain Injury Sedation Protocol**. Consider neuromuscular blockade if increased ICP is associated with dyscoordinated breathing, posturing, excess motor activity or shivering unresponsive to sedation protocol limits. Notify Neurosurgery prior to vecuronium bolus (0.1 mg/kg q 45 minutes).
- 3 If closed ICP reading is 25-29 mm Hg after 2 consecutive hourly readings, or > 30 mm Hg for 1 hourly reading, notify Neurosurgery for escalation to 3% hypertonic saline, or hyperventilation orders. Concurrently, order STAT CT scan of the head, without contrast to rule out mass lesion. In addition, administer mannitol 0.5 gms/kg IV x 1. Repeat mannitol administration if no response in ICP.
- 4 Pentobarbital administration will only be a consideration after all other means of ICP control have been trialed, i.e. paralytics, osmotic therapy, hyperventilation, hypothermia, decompressive craniectomy. Attending Neurosurgeon approval required.

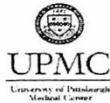
Physician Notifications: Neurosurgery is to be notified prior to any escalation in protocol due to increased ICP, i.e. administration of paralytics, CT scan, mannitol administration. Additional orders must be obtained from Neurosurgery prior to hypertonic saline administration, hyperventilation and pentobarbital administration.

CSF Sampling:

- 1 The External Ventricular Drainage (EVD) system should be closed to the head prior to sampling (see Procedural Manual). Betadine scrub port for 3 minutes and follow sterile procedure.
- 2 Sampling is scheduled q 4 hours for the first 24 hours, and then every 6 hours for the next 4 days, unless EVD is discontinued.
- 3 Obtain 3 ml, if possible, from the tubing closest to the head, and place in red top glass tube.
- 4 Date and time stamp sample and place in a biohazard bag
- 5 Place in 4G freezer immediately following collection for lab pick-up.

This page is NOT a permanent part of the medical record.

Figure 17A Intracranial Hypertension Management Protocol.



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Severe Traumatic Brain Injury: Sedation Protocol -- Physician Order Set

Analgesia- Fentanyl

- ☒ Begin fentanyl infusion at 50 micrograms/hour upon admission to the ICU.
- ☒ PRN dose and indication (this is in addition to the ongoing Fentanyl infusion) Fentanyl 100 micrograms IV q 1 hour prn for ventilator dysynchrony, hyperventilation, posturing, excess motor activity, shivering, episodic hypertension (MAP > 110 mmHg) or episodic tachycardia (HR > 110) or any clinical indicator suggesting unrelieved pain.
- ☒ Increase fentanyl infusion by 50 micrograms/hour every 4 hours to a maximum infusion rate of 200 micrograms per hour if prn Fentanyl boluses > 200 micrograms in preceding 4 hour period.
- ☒ Reduce fentanyl infusion for neuro exam every morning at 6am to 50 micrograms/min unless ICP \geq 25 mmHg; there is an indication for a prn bolus of fentanyl; or the patient is receiving neuromuscular blockers. Maintain infusion at 50 micrograms/kg/min unless additional bolus doses are indicated.

Sedation- Propofol

- ☒ Begin propofol infusion at 20 micrograms/kg/minute upon admission to the ICU.
- ☒ PRN Dose and Indications: Propofol bolus 0.5 mg/kg IV q 1 hour prn for posturing, restlessness, excess motor activity, shivering, episodic hypertension, episodic tachycardia resistant to fentanyl boluses.
- ☒ PRN Dose for Increased ICP: Propofol bolus 0.25 mg/kg IV q 1 hour prn for ICP elevation > 25 mmHg
- ☒ Increase propofol infusion by 10 micrograms/kg/min q 1 hour following any prn propofol bolus to a maximum of 100 micrograms/kg/min.
- ☒ Stop propofol infusion at 7am every day for neuro exam unless ICP > 25, there is an indication for a prn bolus, or the patient is receiving neuromuscular blockers. Observe patient off of propofol and restart infusion at 50% of prior dose if there remains an indication to continue propofol.

Neuromuscular Blockade - Vecuronium

- ☒ Vecuronium 0.1 mg/kg bolus q 45 minutes prn dyscoordinated breathing unresponsive to sedation, intracranial hypertension (ICP > 25 mmHg) associated with posturing, excess motor activity, or shivering unresponsive to 100 micrograms of fentanyl and 0.50 mg/kg bolus of propofol.

Other

- ☒ Hold propofol for hypotension (MAP < 65 mmHg) or vasopressor requirements
- ☒ Obtain triglyceride level daily for all patients on propofol dose > 50 micrograms/kg/min for > 24 hours
- ☒ Notify physician for uncontrollable motor activity, ventilator dysynchrony and the need for vecuronium

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(Signature)

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Figure 18A Sedation Protocol for Head Injury Patients.



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Severe Traumatic Brain Injury: Fluid Resuscitation Protocol -- Physician Order Set
Fluid Resuscitation Protocol Guidelines are on following page**Physician Notifications**

- ☒ Any stops or interruptions in protocol because of adverse effects of fluid administration
☒ Any time vasopressor support is initiated with levophed
☒ Failure to achieve physiological endpoints within the constraints of the protocol

Orders to be implemented if hypotension or low cerebral perfusion pressure occurs

HYPOTENSION (MAP < 65 mmHg)					
	CVP	Challenge Volume	Fluid	Frequency	Maximum Volume
<input checked="" type="checkbox"/>	< 5	1000 ml	Colloid	Bolus	1000 ml
			Sodium Chloride	q 30 min	2000 ml
<input checked="" type="checkbox"/>	5-10	500 ml	Colloid	q 15 min	1000 ml
			Sodium Chloride	q 15 min	1000 ml
<input checked="" type="checkbox"/>	11-12	250 ml	Colloid	q 10 min	500 ml
			Sodium Chloride	q 10 min	500 ml
LOW CEREBRAL PERFUSION PRESSURE (CPP < 60 mmHg)					
	CVP	Challenge Volume	Fluid	Frequency	Maximum Volume
<input checked="" type="checkbox"/>	< 5	1000 ml	Sodium Chloride	q 60 min	2000 ml
	5-10	500 ml	Sodium Chloride	q 60 min	1000 ml
	11-12	No Fluid Challenge, Norepinephrine (Levophed) if MAP < 100 mmHg			

Fluid Challenge and Vasopressor administration details

- ☒ 5% albumin 1000 ml maximum - administer only during first 24 hours after ICU admission.

- ☒ Hetastarch in balanced salt solution (Hextend) 1000 ml maximum/day, start > 24 hours after ICU admission

- ☒ Norepinephrine (Levophed) infusion at 0.1 mcg/kg/min for hypotension or low CPP unresponsive to 1 liter fluid challenge. (CPP < 60 mmHg, CVP > 10 mmHg and MAP < 100 mmHg)
Titrate to MAP 65-70 mmHg or CPP > 60 mmHg.

- ☒ Maximum colloid permitted is 1 liter every 24 hours.
☒ For all colloid challenges, terminate challenge if BP endpoint achieved prior to receiving full challenge volume.
☒ If patient requires vasopressor to achieve physiological endpoints, continue volume challenges up to protocol volume limits and attempt weaning from vasopressor.

(BLOCK Print Name)

(Signature)

Date / Time:

Pager #



0031-01-U

Form ID: PUH-1505 Last Revision Date: 05/18/2005

☐ Order Set Faxed to Pharmacy by:
(name / time)

Unit:



PHYSICIAN ORDER SET

AUTHORIZATION IS GIVEN TO THE PHARMACY TO DISPENSE AND TO THE NURSE TO ADMINISTER THE GENERIC OR CHEMICAL EQUIVALENT WHEN THE DRUG IS FILLED BY THE PHARMACY OF THE UPMC HEALTH SYSTEM HOSPITAL - UNLESS THE PRODUCT NAME IS CIRCLED.

Account Number:

IMPRINT PATIENT IDENTIFICATION HERE

SEVERE TBI ORDERS FLUID RESUSCITATION PROTOCOL

Protocol Goals: The main goals of this protocol are to provide a standardized approach to fluid resuscitation in patients with severe TBI who develop hypotension and/or intracranial hypertension with a low cerebral perfusion pressure.

Protocol Exclusions: TBI patients will be considered ineligible for this protocol if they have or develop ARDS, acute pulmonary edema or acute myocardial infarction.

Protocol Triggers: The patient will be eligible for fluid resuscitation by protocol if they develop hypotension (MAP < 65 mmHg) or a reduction in CPP (CPP < 60 mmHg) due to increased ICP and CVP level is < 12 mmHg. For patients developing reduced CPP as a result of both hypotension and increased ICP, the hypotension pathway will be followed. Patients who require Vasopressors to maintain MAP or CPP endpoints will also be included in this protocol.

Implementation of Fluid Resuscitation

- Once the hypotension or low CPP pathway is triggered, measure and record CVP. The measured CVP level will determine the amount of each volume challenge to be administered, the type of fluid to be administered, the frequency with which boluses are administered and the maximum volume to be administered at each CVP level. ** Fluid challenges are not administered to the patient in this protocol on the basis of CVP measurements unless there is
- 1 hypotension or low CPP.
- For each pathway, fluid is administered until MAP or CPP is restored to the desired endpoints or until the maximum allowable volume has been
- 2 administered, the CVP exceeds 12 mmHg or complications of hypoxemia or pulmonary edema occur.
- When the hypotension pathway has been entered, fluid therapy is initiated first with colloid and then proceeds with Sodium Chloride if after administering the
- 3 maximum allowable amount of colloid (1 liter) the MAP endpoints have not been reached. Colloid is not used for the low CPP pathway.
- If during the course of fluid resuscitation the CVP rises to a higher CVP level but the MAP or CPP endpoints have not been achieved, proceed with
- 4 resuscitation as determined at the new CVP level.

Protocol Details:

Colloid Type: For first 24 hours after injury, the colloid of choice is 5% albumin to avoid potential bleeding risks.

Thereafter, the colloid of choice is Hextend.

Maximum colloid: The maximum allowable colloid permitted by protocol is 1 liter every 24 hours.

- Vasopressors: Levophed is started for persistent hypotension or low CPP after a 1 liter volume challenge or low CPP persists with MAP < 100 and CVP exceeding 10 mmHg.
 - Hypotension: If hypotension remains unresponsive to a 1 liter colloid challenge, begin levophed infusion at 0.1 micrograms/kg/min and titrate to MAP 65-70 mmHg. Continue with Sodium Chloride fluid challenges up to protocol limits while attempting to wean off levophed.
 - Low CPP: If low CPP remains unresponsive to a 1 liter Sodium Chloride challenge begin levophed infusion at 0.1 micrograms/kg/min and titrate to CPP 60-70 mmHg. Continue Sodium Chloride fluid challenges up to protocol limits while attempting to wean off levophed.
 - Low CPP- High CVP: If CPP < 60 mmHg, MAP < 100 mmHg and CVP > 10 mmHg, begin levophed infusion at 0.1 micrograms/kg/min and titrate to CPP 60-70 mmHg.

Protocol Renewal: The protocol is automatically renewed every 24 hours.

Physician Notifications: CCM and Neurosurgery should be notified if MAP or CPP endpoints are not achieved within the volume limits of the protocol, the CVP limits are exceeded, there is a need to initiate vasopressor therapy or hypoxemia or pulmonary edema develops.

This page is NOT a permanent part of the medical record.

Figure 19A Fluid Replacement Protocol for Head Injury Patients

APPENDIX B: DATA DICTIONARY FOR SAS PROGRAM

Data dictionary for SAS file:

<i>Variable</i>	<i>Name</i>	<i>Codes</i>
UID	UID	N.A.
Time	Time	N.A.
Licox value	Licox	N.A.
Serum magnesium level	Mg	N.A.
Fraction of inspired oxygen	FiO2	N.A.
Blood transfusions	RBC	N.A.
Mean Arterial Pressure	ABP_M	N.A.
Intracranial Pressure	ICP	N.A.
Core temperature	T1	N.A.
Cerebral Perfusion Pressure	CPP	N.A.
Magnesium dose	Mginfusion	0=no 1=yes
Magnesium Dose	Magdose	N.A.
Time from Injury to Magnesium Dose	maglag	0=24 hours or less 1=25 to 48 hours
Magnesium protocol	Magproto	0=no 1=yes
Admission protocol	Admisproto	0=no

<i>Variable</i>	<i>Name</i>	<i>Codes</i>
		1=yes
ICP protocol	ICPproto	0=no
		1=yes
Sedation protocol	Sedproto	0=no
		1=yes
Fluid replacement protocol	Fluidproto	0=no
		1=yes
Injury type	Injurytype	0=SAH
		1=SDH
		2=combined
Injury side	injuryside	0=left
		1=right
		2=bilateral
Alsus	Alsus	0=no
		1=yes
Age	Age	N.A
Gender	Gender	0=female
		1=male

<i>Variable</i>	<i>Name</i>	<i>Codes</i>
Complications	complications	0=none 1=nonneurological 2=neurological
GCS	GCS	N.A.
Mechanism of Injury	Mechinjury	0=Motor vehicle 1=Motorcycle 2=Other
Transport	Transport	0=helicopter 1=ambulance
Emergency department drugs	Eddrug	0=none 1=mannitol 2=norepinephrine
Marshall score	Marsh	N.A.
Surgery	Surgery	0=none 1=yes

APPENDIX C: SAS PROGRAMING CODE

```
data thesis;
set thesis;
magdose = .;
if uid=467 and mginfusion=1 then magdose=6 ;
if uid=472 and mginfusion=1 then magdose=6 ;
if uid=472.2 and mginfusion=1 then magdose=2;
if uid=474 and mginfusion=1 then magdose=4;
if uid=474.2 and mginfusion=1 then magdose=4;
if uid=485 and mginfusion=1 then magdose=6;
if uid=502 and mginfusion=1 then magdose=6;
if uid=518 and mginfusion=1 then magdose=4;
if uid=518.2 and mginfusion=1 then magdose=4;
if uid=541 and mginfusion=1 then magdose=4;
if uid=547 and mginfusion=1 then magdose=6;
if uid=548 and mginfusion=1 then magdose=4;
if uid=555 and mginfusion=1 then magdose=2;
if uid=575 and mginfusion=1 then magdose=8;
if uid=576 and mginfusion=1 then magdose=8;
if uid=582 and mginfusion=1 then magdose=8;
if uid=586 and mginfusion=1 then magdose=8;
if uid=592 and mginfusion=1 then magdose=4;
if uid=595 and mginfusion=1 then magdose=8;
if uid=596 and mginfusion=1 then magdose=4;
if uid=596.2 and mginfusion=1 then magdose=4;
if uid=616 and mginfusion=1 then magdose=6;
if uid=616.2 and mginfusion=1 then magdose=8;
if uid=621 and mginfusion=1 then magdose=2;
if mginfusion =0 then magdose=10;
maglag = .;
if uid=467 then maglag=1;
if uid=472 then maglag=0;
if uid=472.2 then maglag=1;
if uid=474 then maglag=0;
if uid=474.2 then maglag=0;
if uid=485 then maglag=0;
if uid=502 then maglag=0;
if uid=518 then maglag=0;
if uid=518.2 then maglag=1;
if uid=541 then maglag=1;
if uid=547 then maglag=0;
if uid=548 then maglag=1;
if uid=555 then maglag=0;
if uid=575 then maglag=0;
if uid=576 then maglag=0;
```



```

if uid=582 then maglag=0;
if uid=586 then maglag=0;
if uid=592 then maglag=1;
if uid=595 then maglag=0;
if uid=596 then maglag=0;
if uid=596.2 then maglag=1;
if uid=616 then maglag=0;
if uid=616.2 then maglag=1;
if uid=621 then maglag=0;

magproto=.;
if uid=467 then magproto=0;
if uid=472 then magproto=0;
if uid=472.2 then magproto=0;
if uid=474 then magproto=0;
if uid=474.2 then magproto=0;
if uid=485 then magproto=0;
if uid=502 then magproto=0;
if uid=518 then magproto=0;
if uid=518.2 then magproto=1;
if uid=541 then magproto=0;
if uid=547 then magproto=0;
if uid=548 then magproto=1;
if uid=555 then magproto=1;
if uid=575 then magproto=1;
if uid=576 then magproto=1;
if uid=582 then magproto=1;
if uid=586 then magproto=1;
if uid=592 then magproto=1;
if uid=595 then magproto=1;
if uid=596 then magproto=0;
if uid=596.2 then magproto=0;
if uid=616 then magproto=0;
if uid=616.2 then magproto=1;
if uid=621 then magproto=0;
admisproto =.;
if uid=467 then admisproto=1;
if uid=472 then admisproto=1;
if uid=472.2 then admisproto=1;
if uid=474 then admisproto=0;
if uid=474.2 then admisproto=0;
if uid=485 then admisproto=1;
if uid=502 then admisproto=1;
if uid=518 then admisproto=1;
if uid=518.2 then admisproto=1;
if uid=541 then admisproto=1;
if uid=547 then admisproto=1;
if uid=548 then admisproto=1;
if uid=555 then admisproto=1;
if uid=575 then admisproto=1;
if uid=576 then admisproto=1;
if uid=582 then admisproto=1;
if uid=586 then admisproto=1;
if uid=592 then admisproto=1;
if uid=595 then admisproto=1;
if uid=596 then admisproto=1;
if uid=596.2 then admisproto=1;

```

```

if uid=616 then admisproto=1;
if uid=616.2 then admisproto=1;
if uid=621 then admisproto=1;
icppproto=.;
if uid=467 then icppproto=1;
if uid=472 then icppproto=1;
if uid=472.2 then icppproto=1;
if uid=474 then icppproto=1;
if uid=474.2 then icppproto=1;
if uid=485 then icppproto=1;
if uid=502 then icppproto=1;
if uid=518 then icppproto=1;
if uid=518.2 then icppproto=1;
if uid=541 then icppproto=0;
if uid=547 then icppproto=1;
if uid=548 then icppproto=1;
if uid=555 then icppproto=1;
if uid=575 then icppproto=0;
if uid=576 then icppproto=0;
if uid=582 then icppproto=1;
if uid=586 then icppproto=1;
if uid=592 then icppproto=1;
if uid=595 then icppproto=1;
if uid=596 then icppproto=1;
if uid=596.2 then icppproto=1;
if uid=616 then icppproto=1;
if uid=616.2 then icppproto=1;
if uid=621 then icppproto=1;
sedproto=.;
if uid=467 then sedproto=1;
if uid=472 then sedproto=1;
if uid=472.2 then sedproto=1;
if uid=474 then sedproto=1;
if uid=474.2 then sedproto=1;
if uid=485 then sedproto=1;
if uid=502 then sedproto=1;
if uid=518 then sedproto=1;
if uid=518.2 then sedproto=1;
if uid=541 then sedproto=1;
if uid=547 then sedproto=1;
if uid=548 then sedproto=1;
if uid=555 then sedproto=1;
if uid=575 then sedproto=1;
if uid=576 then sedproto=1;
if uid=582 then sedproto=1;
if uid=586 then sedproto=1;
if uid=592 then sedproto=1;
if uid=595 then sedproto=1;
if uid=596 then sedproto=1;
if uid=596.2 then sedproto=1;
if uid=616 then sedproto=1;
if uid=616.2 then sedproto=1;
if uid=621 then sedproto=1;
fluidproto =.;
if uid=467 then fluidproto=1;
if uid=472 then fluidproto=1;
if uid=472.2 then fluidproto=1;

```

```

if uid=474 then fluidproto=1;
if uid=474.2 then fluidproto=1;
if uid=485 then fluidproto=1;
if uid=502 then fluidproto=0;
if uid=518 then fluidproto=1;
if uid=518.2 then fluidproto=1;
if uid=541 then fluidproto=0;
if uid=547 then fluidproto=1;
if uid=548 then fluidproto=1;
if uid=555 then fluidproto=0;
if uid=575 then fluidproto=0;
if uid=576 then fluidproto=0;
if uid=582 then fluidproto=1;
if uid=586 then fluidproto=1;
if uid=592 then fluidproto=1;
if uid=595 then fluidproto=0;
if uid=596 then fluidproto=1;
if uid=596.2 then fluidproto=1;
if uid=616 then fluidproto=1;
if uid=616.2 then fluidproto=1;
if uid=621 then fluidproto=1;
injurytype=.;
if uid=467 then injurytype=2;
if uid=472 then injurytype=0;
if uid=472.2 then injurytype=1;
if uid=474 then injurytype=1;
if uid=474.2 then injurytype=1;
if uid=485 then injurytype=1;
if uid=502 then injurytype=1;
if uid=518 then injurytype=1;
if uid=518.2 then injurytype=1;
if uid=541 then injurytype=1;
if uid=547 then injurytype=0;
if uid=548 then injurytype=0;
if uid=555 then injurytype=0;
if uid=575 then injurytype=1;
if uid=576 then injurytype=0;
if uid=582 then injurytype=1;
if uid=586 then injurytype=0;
if uid=592 then injurytype=2;
if uid=595 then injurytype=0;
if uid=596 then injurytype=0;
if uid=596.2 then injurytype=0;
if uid=616 then injurytype=2;
if uid=616.2 then injurytype=2;
if uid=621 then injurytype=2;
injuryside =.;
if uid=467 then injuryside=1;
if uid=472 then injuryside=1;
if uid=472.2 then injuryside=1;
if uid=474 then injuryside=0;
if uid=474.2 then injuryside=0;
if uid=485 then injuryside=2;
if uid=502 then injuryside=0;
if uid=518 then injuryside=0;
if uid=518.2 then injuryside=0;
if uid=541 then injuryside=2;

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```

if uid=547 then injuryside=0;
if uid=548 then injuryside=1;
if uid=555 then injuryside=2;
if uid=575 then injuryside=2;
if uid=576 then injuryside=2;
if uid=582 then injuryside=2;
if uid=586 then injuryside=0;
if uid=592 then injuryside=0;
if uid=595 then injuryside=1;
if uid=596 then injuryside=1;
if uid=596.2 then injuryside=1;
if uid=616 then injuryside=2;
if uid=616.2 then injuryside=2;
if uid=621 then injuryside=2;
alsius =.;
if uid=467 then alsius=0;
if uid=472 then alsius=0;
if uid=472.2 then alsius=0;
if uid=474 then alsius=0;
if uid=474.2 then alsius=0;
if uid=485 then alsius=0;
if uid=502 then alsius=0;
if uid=518 then alsius=0;
if uid=518.2 then alsius=0;
if uid=541 then alsius=0;
if uid=547 then alsius=0;
if uid=548 then alsius=0;
if uid=555 then alsius=0;
if uid=575 then alsius=1;
if uid=576 then alsius=1;
if uid=582 then alsius=1;
if uid=586 then alsius=1;
if uid=592 then alsius=0;
if uid=595 then alsius=1;
if uid=596 then alsius=0;
if uid=596.2 then alsius=0;
if uid=616 then alsius=0;
if uid=616.2 then alsius=0;
if uid=621 then alsius=0;
age=.;
if uid=467 then age=18;
if uid=472 then age=51;
if uid=472.2 then age=51;
if uid=474 then age=22;
if uid=474.2 then age=22;
if uid=485 then age=22;
if uid=502 then age=16;
if uid=518 then age=37;
if uid=518.2 then age=37;
if uid=541 then age=23;
if uid=547 then age=40;
if uid=548 then age=50;
if uid=555 then age=44;
if uid=575 then age=29;
if uid=576 then age=28;
if uid=582 then age=19;
if uid=586 then age=18;

```

```

if uid=592 then age=21;
if uid=595 then age=43;
if uid=596 then age=30;
if uid=596.2 then age=30;
if uid=616 then age=45;
if uid=616.2 then age=45;
if uid=621 then age=20;
gender =.;
if uid=467 then gender=1;
if uid=472 then gender=1;
if uid=472.2 then gender=1;
if uid=474 then gender=1;
if uid=474.2 then gender=1;
if uid=485 then gender=1;
if uid=502 then gender=0;
if uid=518 then gender=1;
if uid=518.2 then gender=1;
if uid=541 then gender=1;
if uid=547 then gender=1;
if uid=548 then gender=1;
if uid=555 then gender=1;
if uid=575 then gender=1;
if uid=576 then gender=1;
if uid=582 then gender=1;
if uid=586 then gender=1;
if uid=592 then gender=1;
if uid=595 then gender=0;
if uid=596 then gender=1;
if uid=596.2 then gender=1;
if uid=616 then gender=1;
if uid=616.2 then gender=1;
if uid=621 then gender=1;
complications =.;
if uid=467 then complications=1;
if uid=472 then complications=2;
if uid=472.2 then complications=2;
if uid=474 then complications=1;
if uid=474.2 then complications=1;
if uid=485 then complications=1;
if uid=502 then complications=1;
if uid=518 then complications=1;
if uid=518.2 then complications=1;
if uid=541 then complications=0;
if uid=547 then complications=1;
if uid=548 then complications=1;
if uid=555 then complications=0;
if uid=575 then complications=1;
if uid=576 then complications=1;
if uid=582 then complications=2;
if uid=586 then complications=1;
if uid=592 then complications=0;
if uid=595 then complications=0;
if uid=596 then complications=0;
if uid=596.2 then complications=1;
if uid=616 then complications=1;
if uid=616.2 then complications=1;
if uid=621 then complications=1;

```

```

gcs=.;
if uid=467 then gcs=4;
if uid=472 then gcs=4;
if uid=472.2 then gcs=4;
if uid=474 then gcs=7;
if uid=474.2 then gcs=7;
if uid=485 then gcs=4;
if uid=502 then gcs=4;
if uid=518 then gcs=7;
if uid=518.2 then gcs=7;
if uid=541 then gcs=7;
if uid=547 then gcs=7;
if uid=548 then gcs=7;
if uid=555 then gcs=4;
if uid=575 then gcs=7;
if uid=576 then gcs=4;
if uid=582 then gcs=.;
if uid=586 then gcs=6;
if uid=592 then gcs=8;
if uid=595 then gcs=8;
if uid=596 then gcs=8;
if uid=596.2 then gcs=8;
if uid=616 then gcs=3;
if uid=616.2 then gcs=3;
if uid=621 then gcs=3;

mechinjury =.;
if uid=467 then mechinjury=0;
if uid=472 then mechinjury=0;
if uid=472.2 then mechinjury=0;
if uid=474 then mechinjury=0;
if uid=474.2 then mechinjury=0;
if uid=485 then mechinjury=0;
if uid=502 then mechinjury=0;
if uid=518 then mechinjury=1;
if uid=518.2 then mechinjury=1;
if uid=541 then mechinjury=1;
if uid=547 then mechinjury=1;
if uid=548 then mechinjury=0;
if uid=555 then mechinjury=0;
if uid=575 then mechinjury=1;
if uid=576 then mechinjury=1;
if uid=582 then mechinjury=0;
if uid=586 then mechinjury=2;
if uid=592 then mechinjury=2;
if uid=595 then mechinjury=2;
if uid=596 then mechinjury=2;
if uid=596.2 then mechinjury=0;
if uid=616 then mechinjury=1;
if uid=616.2 then mechinjury=1;
if uid=621 then mechinjury=0;
transport=.;
if uid=467 then transport=1;
if uid=472 then transport=0;
if uid=472.2 then transport=0;
if uid=474 then transport=0;
if uid=474.2 then transport=0;

```

```

if uid=485 then transport=0;
if uid=502 then transport=0;
if uid=518 then transport=0;
if uid=518.2 then transport=0;
if uid=541 then transport=0;
if uid=547 then transport=0;
if uid=548 then transport=1;
if uid=555 then transport=0;
if uid=575 then transport=0;
if uid=576 then transport=0;
if uid=582 then transport=0;
if uid=586 then transport=0;
if uid=592 then transport=0;
if uid=595 then transport=0;
if uid=596 then transport=0;
if uid=596.2 then transport=0;
if uid=616 then transport=0;
if uid=616.2 then transport=0;
if uid=621 then transport=0;
eddrug=.;
if uid=467 then eddrug=1;
if uid=472 then eddrug=0;
if uid=472.2 then eddrug=0;
if uid=474 then eddrug=0;
if uid=474.2 then eddrug=0;
if uid=485 then eddrug=2;
if uid=502 then eddrug=1;
if uid=518 then eddrug=0;
if uid=518.2 then eddrug=0;
if uid=541 then eddrug=0;
if uid=547 then eddrug=0;
if uid=548 then eddrug=0;
if uid=555 then eddrug=1;
if uid=575 then eddrug=0;
if uid=576 then eddrug=0;
if uid=582 then eddrug=0;
if uid=586 then eddrug=0;
if uid=592 then eddrug=0;
if uid=595 then eddrug=1;
if uid=596 then eddrug=0;
if uid=596.2 then eddrug=0;
if uid=616 then eddrug=0;
if uid=616.2 then eddrug=0;
if uid=621 then eddrug=0;
marsh=.;
if uid=467 then marsh=3;
if uid=472 then marsh=2;
if uid=472.2 then marsh=2;
if uid=474 then marsh=2;
if uid=474.2 then marsh=2;
if uid=485 then marsh=3;
if uid=502 then marsh=4;
if uid=518 then marsh=3;
if uid=518.2 then marsh=3;
if uid=541 then marsh=2;
if uid=547 then marsh=.;
if uid=548 then marsh=2;

```

```

if uid=555 then marsh=.;
if uid=575 then marsh=2;
if uid=576 then marsh=2;
if uid=582 then marsh=.;
if uid=586 then marsh=.;
if uid=592 then marsh=.;
if uid=595 then marsh=3;
if uid=596 then marsh=.;
if uid=596.2 then marsh=2;
if uid=616 then marsh=.;
if uid=616.2 then marsh=.;
if uid=621 then marsh=.;
surgery =.;
if uid=467 then surgery=1;
if uid=472 then surgery=1;
if uid=472.2 then surgery=1;
if uid=474 then surgery=1;
if uid=474.2 then surgery=1;
if uid=485 then surgery=1;
if uid=502 then surgery=1;
if uid=518 then surgery=1;
if uid=518.2 then surgery=1;
if uid=541 then surgery=1;
if uid=547 then surgery=1;
if uid=548 then surgery=1;
if uid=555 then surgery=0;
if uid=575 then surgery=1;
if uid=576 then surgery=1;
if uid=582 then surgery=1;
if uid=586 then surgery=1;
if uid=592 then surgery=1;
if uid=595 then surgery=0;
if uid=596 then surgery=1;
if uid=596.2 then surgery=1;
if uid=616 then surgery=0;
if uid=616.2 then surgery=0;
if uid=621 then surgery=0;
gos3=.;
if uid=467 then gos3=1;
if uid=472 then gos3=1;
if uid=472.2 then gos3=1;
if uid=474 then gos3=3;
if uid=474.2 then gos3=1;
if uid=485 then gos3=1;
if uid=502 then gos3=1;
if uid=518 then gos3=3;
if uid=518.2 then gos3=3;
if uid=541 then gos3=5;
if uid=547 then gos3=4;
if uid=548 then gos3=4;
if uid=555 then gos3=2;
if uid=575 then gos3=3;
if uid=576 then gos3=1;
if uid=582 then gos3=1;
if uid=586 then gos3=3;
if uid=592 then gos3=.;
if uid=595 then gos3=3;

```



```

if uid=596 then gos3=4;
if uid=596.2 then gos3=4;
if uid=616 then gos3=5;
if uid=616.2 then gos3=5;
if uid=621 then gos3=.;
gos6=.;
if uid=467 then gos6=1;
if uid=472 then gos6=1;
if uid=472.2 then gos6=1;
if uid=474 then gos6=.;
if uid=474.2 then gos6=1;
if uid=485 then gos6=1;
if uid=502 then gos6=1;
if uid=518 then gos6=4;
if uid=518.2 then gos6=4;
if uid=541 then gos6=5;
if uid=547 then gos6=3;
if uid=548 then gos6=4;
if uid=555 then gos6=3;
if uid=575 then gos6=.;
if uid=576 then gos6=1;
if uid=582 then gos6=1;
if uid=586 then gos6=3;
if uid=592 then gos6=.;
if uid=595 then gos6=3;
if uid=596 then gos6=4;
if uid=596.2 then gos6=4;
if uid=616 then gos6=5;
if uid=616.2 then gos6=5;
if uid=621 then gos6=.;
gos12=.;
if uid=467 then gos12=1;
if uid=472 then gos12=1;
if uid=472.2 then gos12=1;
if uid=474 then gos12=.;
if uid=474.2 then gos12=1;
if uid=485 then gos12=1;
if uid=502 then gos12=1;
if uid=518 then gos12=4;
if uid=518.2 then gos12=4;
if uid=541 then gos12=5;
if uid=547 then gos12=3;
if uid=548 then gos12=4;
if uid=555 then gos12=3;
if uid=575 then gos12=5;
if uid=576 then gos12=1;
if uid=582 then gos12=1;
if uid=586 then gos12=3;
if uid=592 then gos12=.;
if uid=595 then gos12=4;
if uid=596 then gos12=.;
if uid=596.2 then gos12=.;
if uid=616 then gos12=5;
if uid=616.2 then gos12=5;
if uid=621 then gos12=.;
gos24=.;
if uid=467 then gos24=1;

```

```

if uid=472 then gos24=1;
if uid=472.2 then gos24=1;
if uid=474 then gos24=. ;
if uid=474.2 then gos24=1;
if uid=485 then gos24=1;
if uid=502 then gos24=1;
if uid=518 then gos24=. ;
if uid=518.2 then gos24=. ;
if uid=541 then gos24=. ;
if uid=547 then gos24=. ;
if uid=548 then gos24=5;
if uid=555 then gos24=. ;
if uid=575 then gos24=5;
if uid=576 then gos24=1;
if uid=582 then gos24=1;
if uid=586 then gos24=. ;
if uid=592 then gos24=. ;
if uid=595 then gos24=. ;
if uid=596 then gos24=. ;
if uid=596.2 then gos24=. ;
if uid=616 then gos24=. ;
if uid=616.2 then gos24=. ;
if uid=621 then gos24=. ;
run;
proc univariate data =thesis normal;
var licox;
histogram licox/normal;
run;
proc sort data=thesis;
by gender;
run;
proc mixed data =thesis covtest;
by gender;
class mginfusion;
model licox= mginfusion time/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time fio2/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time cpp/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;

```

```

class mginfusion;
model licox= mginfusion time magdose/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time maglag/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time injurytype/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time injuryside/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time gcs/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time age/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time marsh/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;

```

```

model licox= mginfusion time surgery/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
class mginfusion;
by gender;
model licox= mginfusion time complications/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time magproto/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time icppproto/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time sedproto/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time fluidproto/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time fio2 cpp magdose gcs complications/corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc mixed data =thesis covtest;
by gender;
class mginfusion;
model licox= mginfusion time fio2 magdose cpp/ corrb cl;

```

```

lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / local type=ar(1);
run;
proc univariate data=norm normal;
by gender;
var resid;
histogram resid/normal;
run;
proc univariate data=thesis normal;
by gender;
var magdose;
histogram magdose/normal;
run;
proc sort data= thesis;
by gender;
run;
proc gplot data=thesis;
by gender mginfusion;
symbol v=circle c=red interpol=box;
plot Licox*fio2;
run;
proc mixed data =thesis;
by gender;
class mginfusion;
model licox= mginfusion time fio2 cpp/ outp =norm residual corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=un;
repeated / type=ar(1);
run;
proc mixed data =thesis order =internal;
by gender ;
class magdose;
model licox= magdose time fio2 cpp/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=un;
repeated / type=ar(1);
run;

proc mixed data =thesis covtest;
by gender;
class mginfusion;
model licox= mginfusion time/ corrb cl;
lsmeans mginfusion /adjust=bon;
random intercept/subject=uid type=ar(1);
repeated / type=ar(1);
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;

proc mixed data =thesis order =internal covtest;

```

```

by gender ;
class magdose;
model licox= magdose injuryside time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose injurytype time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose gcs time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose age time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose marsh time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose surgery time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose magproto time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;

```

```

class magdose;
model licox= magdose icpproto time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose fluidproto time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose sedproto time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose cpp time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose fio2 time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;
proc mixed data =thesis order =internal covtest;
by gender ;
class magdose;
model licox= magdose cpp fio2 time/ corrb cl;
lsmeans magdose /adjust=bon;
random intercept/subject=uid type=ar(1) g;
repeated / type=ar(1) ;
run;

```

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